



# ACTA RADIOLOGICA

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FEBRUARY APRIL JUNE AUGUST OCTOBER DECEMBER

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## ARMAMENTARIUM FOR RADIUM TREATMENT OF CARCINOMA OF THE UTERINE CERVIX

by

O. KJELLGREN and I. RAGNHULT

Several different types of radium applicators have been developed since the radium treatment of carcinoma of the uterine cervix has become the method of choice. Radium therapy was previously extensively employed but since the introduction of the supervoltage therapy its use in primary treatment has become less general. It is however still considered the best primary method of dealing with most cases of cancer of the uterine cervix.

All means of applying radium in the treatment of carcinoma of the cervix of the uterus have derived from one of two fundamental methods: the Paris or the Stockholm method. Several of the current local radiation procedures in this condition are illustrated in Fig. 1.

The Paris method, a protracted low intensity technique of radium treatment, was devised in the beginning of the nineteen twenties by REGAUD et coll. at the Radium Institute, Paris. It makes use of small quantities of radium applied for the fairly long time of about 5 days, the total dose amounting to about 8 000 mgh.

The Manchester method was developed from the Paris method, the main feature is the delivery of a predetermined dose to arbitrarily defined points in the pelvis independently of the arrangement of the applicators, it entails

From the Gynecologic Section (Director Herman Leksner) of the Department of Radiotherapy and from the Department of Radiophysics (Director Sven Benner) University of Gothenburg, Sweden. Submitted for publication 14 May 1962.

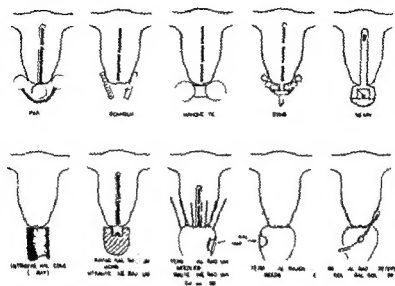


Fig 1 After GRAHAM 1927

differential loading of the applicators dependent upon their size and length. The optimal dose at point A, defined as 2 cm lateral to the uterine canal and 2 cm above the vaginal fornix, has been determined as 7 500 to 8 000 r in two treatments given with an interval of one week (TOD 1941, TOD & MERFIDITH 1938).

The Stockholm method was originally devised by FORSELL & HEYMAN and has been further developed by KOTTMEIER at Radiumhemmet. The technique is based on repeated treatments with fairly large amounts of radium for a relatively short time, a number of different applicators being used. Advantage is taken of the possibilities of selecting the treatment with due regard to the type of the tumour and its spread, the patient's general condition and so on. The length of the intrauterine applicators depends on the length of the uterus. The applicators as a rule are permanently loaded, contain from 53 to 88 mg radium and are so designed that the dose rate 2 cm from the center of the applicator is about 75 r/h. The vaginal applicators, most of which are also permanently loaded, vary in shape and size and mostly contain 60 to 80 mg radium; the radium is usually spread towards the lateral parts of the boxes. The time of treatment generally amounts to about 27 hours at each of two sittings, 3 weeks apart. The total filtration is equivalent to 2 to 3 mm of lead. The dose at the bladder and the rectum is checked by dose measurements, making it possible to avoid overdosage in these organs by cutting down the treatment time when the dose rate is too high. The optimal total dose to the rectum from the radium is 4 000 r and to the bladder about 5 500 r. These doses are generally not exceeded in early stages of carcinoma of the cervix.

but up to 6 000 r may be given to the rectum in advanced stages (KOTTMEIER 1959)

The dose from the intrauterine applicator may be raised by increasing the time of treatment or the amount of radium. The diameter of the applicator is increased to 13 mm from the usual 7 mm in these cases, in order to avoid an excessive dose to the uterine wall. Experience has shown that dilatation of the cervical canal to Hegar 13 may generally be made without difficulty. A higher intrauterine dose is usually given in cases of endocervical carcinoma, paracervical growth, palpable metastases at the pelvic wall, or in cases with a narrow vagina. The vaginal dose must then be correspondingly decreased. Three weeks after the second application, roentgen or telecobalt treatment towards the parametria and pelvic walls is generally administered by the split field technique with two anterior and two posterior portals. Primary roentgen or telecobalt treatment through one large anterior portal, and one or two posterior portals, is given only in advanced cases or in cases with large cauliflower tumours. Perineal portals may also be used in the latter condition.

The dose administered to the cervix amounts to about 20 000 r but much less is received by the pelvic walls. Provided the intrauterine radium is not applied as far down as the external os, the dose at point A with the current Stockholm method amounts to about 6 000 r. With the radium at the external os, the dose to the cervix at the rectum, and at point A increases, however. The dose on the pelvic walls from the intracavitary radium amounts to between 610 and 2 430 r, provided the uterus is situated in the center of the pelvis. The obturator nerve receives about 1 335 r, 60 to 70 % of which is from the intrauterine radium (KOTTMEIER 1953).

Detailed studies of the dose distribution in the pelvis with the Stockholm method have been made by KOTTMEIER (1951 and 1953) and WALSTAM (1954).

A number of special applicators for radium treatment of carcinoma of the cervix have been described and include Ernst's applicator, Neary's applicator, and the Buffalo applicator used at Roswell Park Memorial Institute. Interstitial radium needles in the tumour combined with intrauterine radium or  $\text{Co}^{60}$ , an intravaginal radium bomb combined with intrauterine radium or intravaginal roentgen irradiation through a vaginal cone are other methods of local radiologic treatment. (For references see GRAHAM et coll. 1962.)

It is of great importance to be familiar with the method used and to be aware of the dose delivered to the different parts of the tumour and the pelvic organs regardless of which method is being used.

### Armamentarium

A system of permanently loaded applicators for the radium treatment of carcinoma of the uterine cervix have been developed during recent years in our department, the applicators being similar to those used in the Stockholm

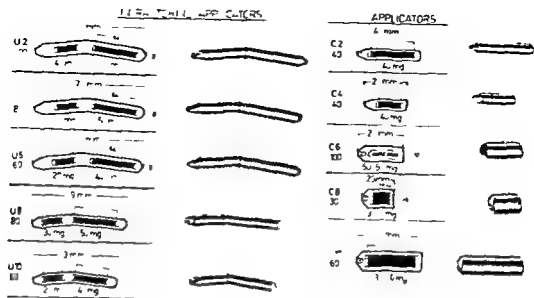


Fig 2

method. The dose rate in r/h at a point 2 cm from the center of the intrauterine applicators is however not constant but numerically equal to the radium content in mg.

Primary radium treatment of carcinoma of the cervix with this armamentarium is generally given in three applications 13 to 14 days apart. The interval is adjusted so that the second and third treatment will be administered at the time when the radiation reaction in the vaginal smear from the preceding treatment has reached its peak (KJELLGREN 1958). If the tumour is confined to the portio or the vagina the first two treatments usually consist of combined intrauterine and vaginal applications and the third only a vaginal application. An intrauterine application is given at the third treatment if the tumour is of endocervical origin or has a large paracervical spread.

Five different intrauterine applicators (U2, U4, U6, U8 and U10) are used. These are permanently loaded with 60, 80 or 100 mg radium and vary in length from 53 to 70 mm. The applicators C2 and C4, each containing 10 mg radium, are used for applications in cervical stumps. One applicator (C6), containing 100 mg radium, and one small (C8) and one large (C10) cylindrical applicators, containing 30 mg and 60 mg of radium respectively, are used for applications to craters. The intrauterine applicators U2 to U10, with a bent knee of 13°, and the applicators C2 to C10 are made of stainless steel. The corporal part contains a larger quantity of radium than the cervical part. The length of the applicators, the diameter, the amount of radium and the active length are given in Fig 2. Attention should be paid to the fact that the radium in the cervical part of the applicator does not reach to the lower end.

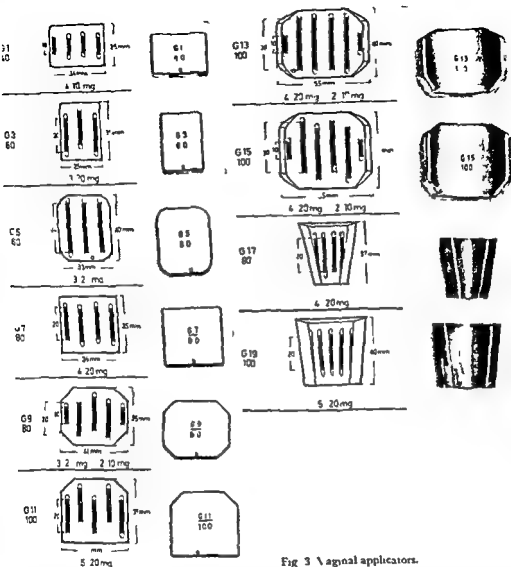
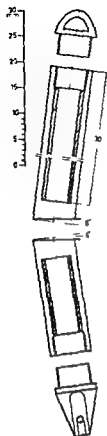


Fig 3 \ vaginal applicators.

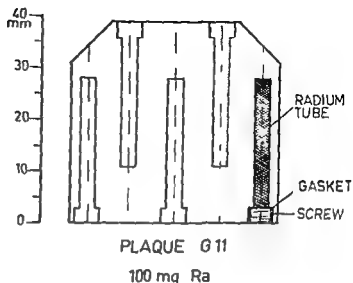
which means that with the applicator pushed up to the fundus no radium is contained in 1.5 to 2 cm of the lower part of the cervix. The isodose curves do not therefore surround the applicators symmetrically but are displaced more towards the corporal end (Figs 6 to 15).

Six flat (G1, G3, G5, G7, G9 and G11) and four curved plaques (G13, G15, G17 and G19) are used for vaginal applications. Some have cut-off corners in order to fit into the vaginal fornices. The two plaques G13 and G15 are slightly curved in order to accommodate large tumours or a large bulky portion of a wide vagina. The curved plaques G17 and G19 are segments of the surface of





INTRAUTERINE APPLICATOR U2  
100 mg Ra



Figs 4 and 5 Constructional details of an intrauterine and a vaginal applicator

a truncated cone and are designed to cover tumours growing down into the vagina. The plaques are loaded with 40, 60, 80 or 100 mg of radium.

The vaginal plaques, with the exception of G17 and G19, are manufactured from stainless steel and have a thickness of 8 mm. The other dimensions are given in Fig. 3. Plaques G17 and G19 are made of Monel metal. The radium tubes are inserted in drilled holes and sealed off by 0.5 mm rubber gaskets and stainless steel screws.

The total filtering equivalent of both the intrauterine and the vaginal applicators is 3 mm Pb. Constructional details of an intrauterine and vaginal applicator are presented in Figs 4 and 5.

### Measurement of the dose distribution around the applicators

The isodose curves for the intrauterine and vaginal applicators were measured in a water phantom with a scintillation detector, fitted with a small anthracene

crystal 3 mm in diameter, and mounted in a long well polished aluminium tube to serve as light pipe between the crystal and the photo-cathode. The scintillation detector was moved along the isodose curves by means of an automatic isodose plotter developed by LARSSON et coll. The movements of the detector were reproduced by a pen that drew the isodose curves on paper.

The isodose distribution was measured in four different planes for all the vaginal plaques, excepting G13 and G15 which were measured in three planes only. The intrauterine applicators were measured in two planes and the small straight applicators in only one plane. The measuring planes were chosen to facilitate clinical evaluation of the dose distribution in the uterus, vagina and the tumour, plane m gives the dose rate 2 mm from the applicator, plane n the dose rate 2 cm above the plane of the radium tubes, and planes k and l give the dose distributions in the frontal and the sagittal planes respectively (cf Fig 21).

The diagrams indicate that the different intrauterine applicators give about 1 000 r per 1 000 mgh at a distance of 2 cm from the center of the applicators. The different vaginal plaques produce about 1 200 to 1 300 r per 1 000 mgh 2 cm above the surface.

All these applicators are readily sterilized and being permanently loaded need little handling which reduces the total radiation hazards. Dose estimations may be made by means of isodose diagrams which are available in standardized planes around the applicators. A system of preloaded applicators with a fixed radium distribution somewhat decreases the possibility of modifying any one treatment.

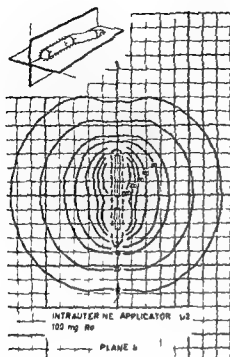


Fig 6

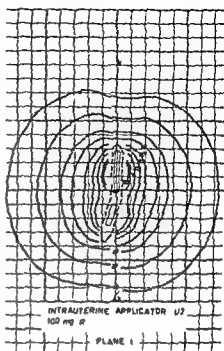


Fig 7

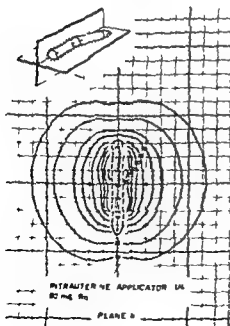


Fig 8

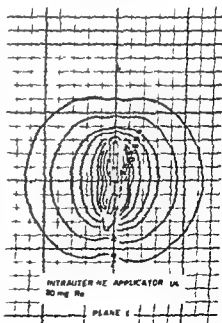


Fig 9

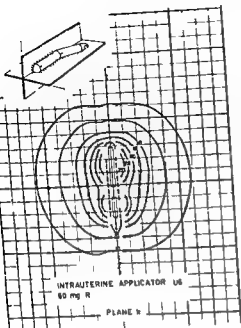


Fig 10

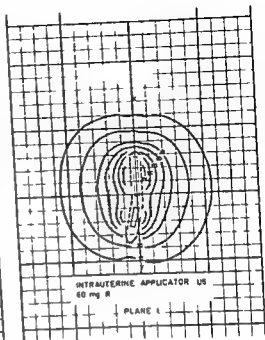


Fig 11

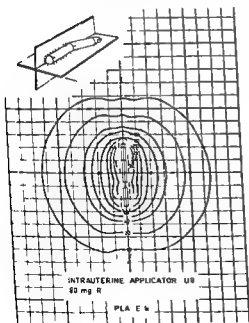


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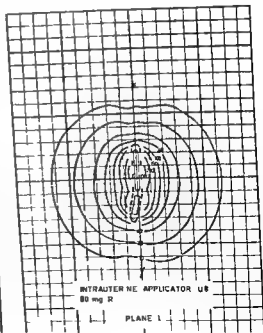


Fig 13

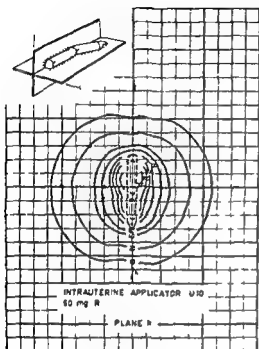


Fig 14

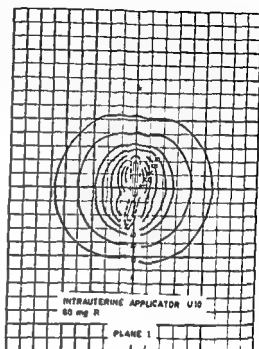


Fig 15

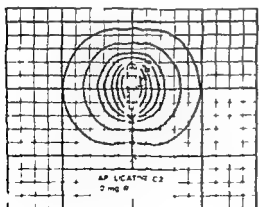


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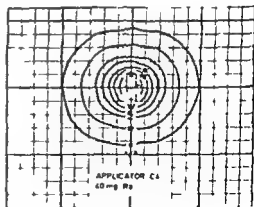


Fig 17

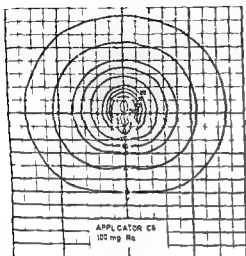


Fig 18

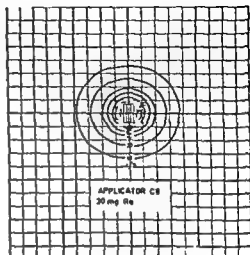


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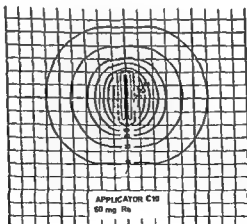


Fig 20

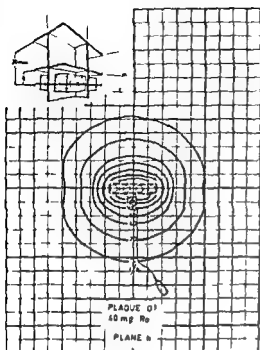


Fig 21

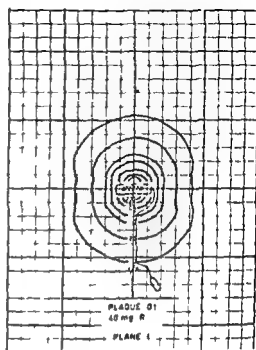


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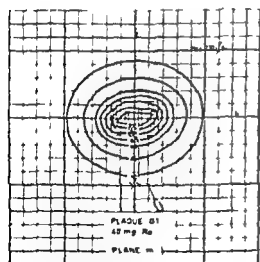


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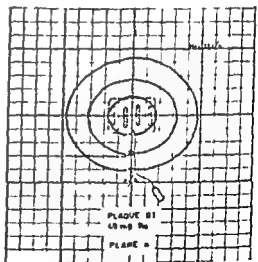


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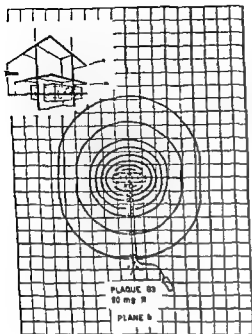


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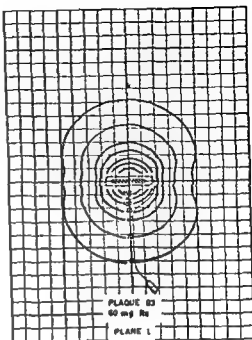


Fig 26

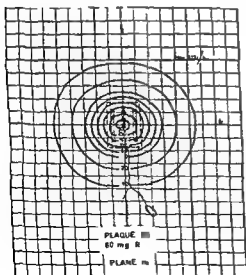


Fig 27

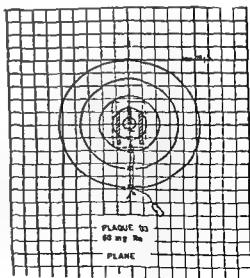


Fig 28



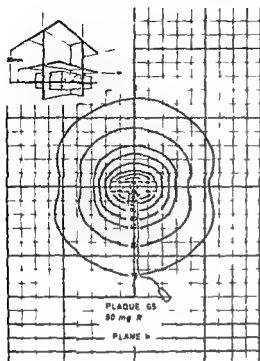


Fig 29

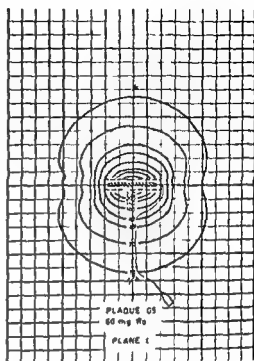


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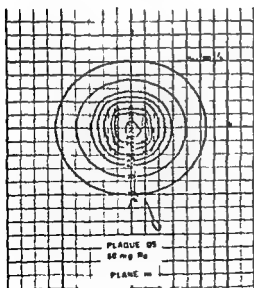


Fig 31

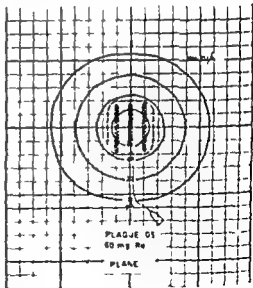


Fig 3

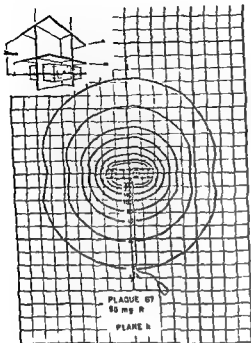


Fig 33

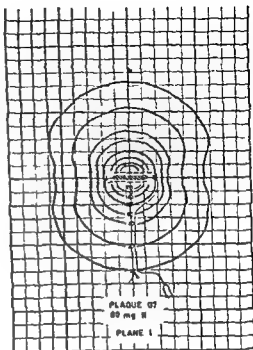


Fig 34

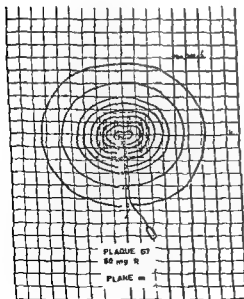


Fig 35

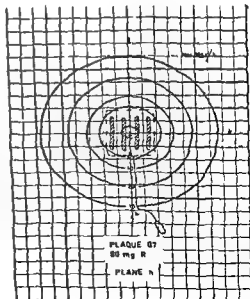


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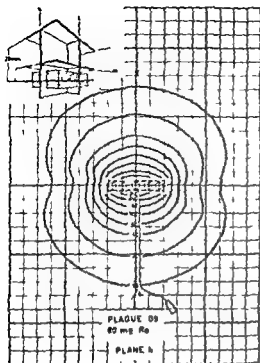


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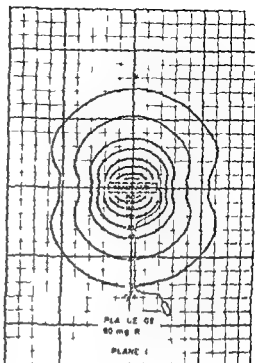


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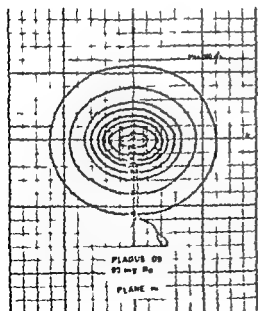


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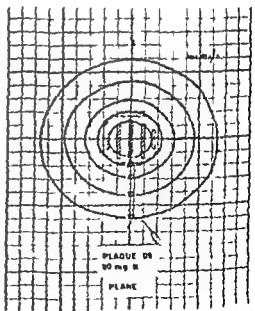


Fig 40

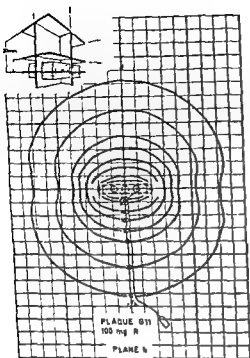


Fig 41

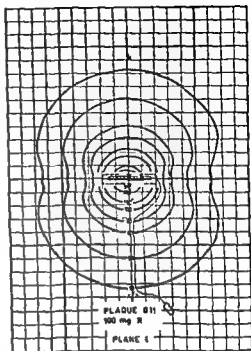


Fig 42

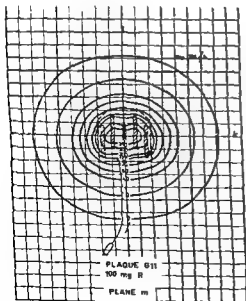


Fig 43

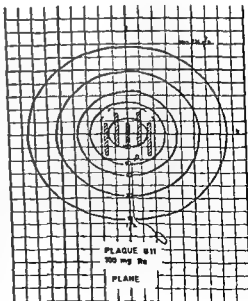


Fig 44

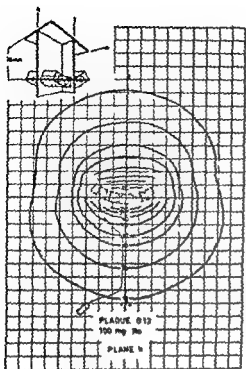


Fig. 43

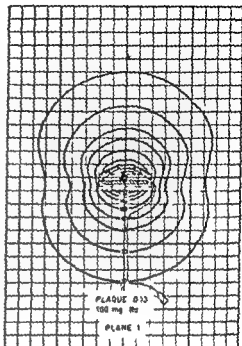


Fig. 44

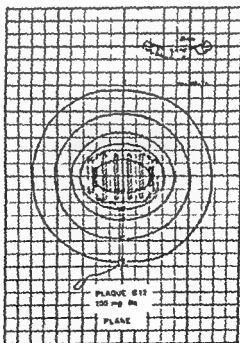


Fig. 45

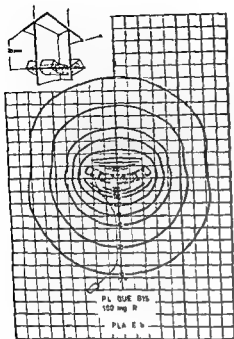


Fig 48

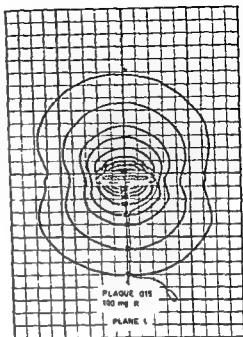


Fig 49

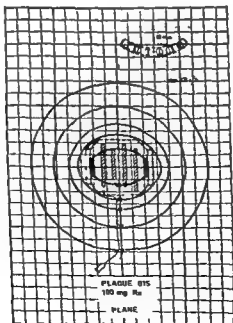


Fig 50

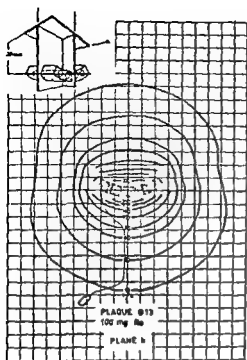


Fig 45

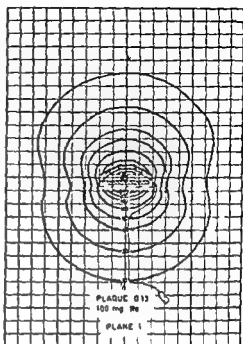


Fig 46

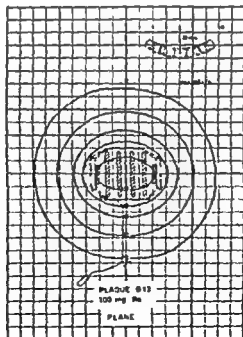


Fig 47

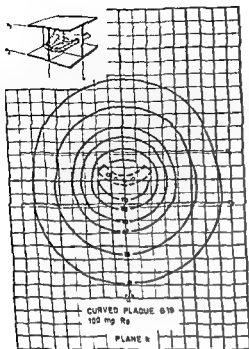


Fig 55

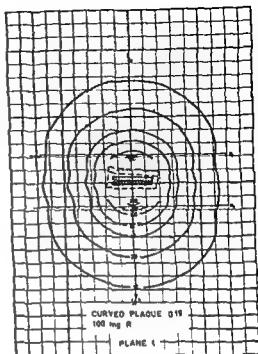


Fig 56

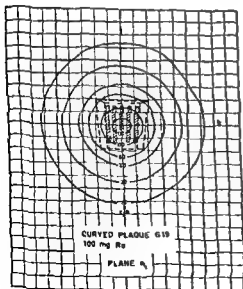


Fig 57

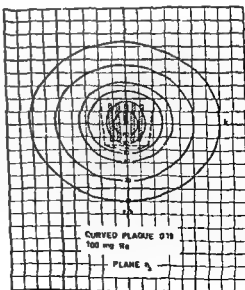


Fig 58



## SUMMARY

A system of permanently loaded applicators for the treatment of carcinoma of the cervix of the uterus is described. Isodose curves in different planes around the applicators are presented.

## ZUSAMMENFASSUNG

Ein System von dauernd geladenen Radiumeinlagen zur Behandlung des Cervixkarzinoms wird beschrieben. Die Arbeit enthält die nötigen Isodosenkurven in verschiedenen Ebenen.

## RÉSUMÉ

Les auteurs décrivent un système d'applicateurs chargés en permanence pour la curie thérapie du cancer du col de l'utérus. Ils présentent les courbes isodoses dans différents plans autour des applicateurs.

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## AUTORADIOGRAPHIC STUDIES OF THE TESTIS AND THE EPIDIDYMIS IN MAN AFTER INCUBATION WITH RADIOACTIVE ZINC IN VITRO

by

KARL EKBOM and BENGT WETTERDAL

The spermatozoa in man have been found to have a particularly high content of zinc compared to other tissues (MAWSON & FISCHER 1953 and BIRNBAUM HALL & LEE 1961). Very little however seems to be known about the localization of zinc in the male reproductive organs and of this physiologic importance. The present investigations on the distribution of zinc in the testis and in the epididymus were carried out in an attempt to gain further information concerning this matter.

Autoradiographic studies on the testes in rats by WETTERDAL (1958) demonstrated that the  $^{65}\text{Zn}$  administered was concentrated in the seminiferous tubules. Scintillation measurements and autoradiography further indicated that the spermatozoa took up the isotope in the seminiferous tubules and with a high amount of  $^{65}\text{Zn}$  were transported through the sperm transport system to the ejaculate.

MILLAP, ELCOAT & FISCHER & MAWSON (1960) suggested that the incorporation of large amounts of zinc in the spermatozoa is essential for their development and for the maintenance of the germinal epithelium.

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MILLAR, VINCENT & MASON (1961) studied the localization of  $^{67}\text{Zn}$  in different rat tissues by autoradiography and suggested that it is slowly incorporated into the spermatozoa during their development in the testes. They found like WETTERDAL, that the spermatozoa progressed from the testes through the epididymal ducts with the radioactive zinc.

DANIEL, HADDAD, PROUT & WHITMORE (1956) and PROUT, SIERP & WHITMORE (1959) injected  $^{67}\text{Zn}$  intravenously in human subjects suffering from various urologic disorders. The amount of  $^{67}\text{Zn}$  in the different organs and tissues removed was studied by scintillation measurements. DANIEL *et coll* (1956) were able to produce an autoradiograph of a prostatic adenoma; no autoradiographs of the testes and the epididymes were obtained, however.

$^{67}\text{Zn}$  seems at present to be the only radioactive zinc isotope readily available for experimental studies. Autoradiographic detection of  $^{67}\text{Zn}$  is, however, rather difficult because of the small amount (1.6%) of beta rays in the decay scheme. This fact and the relatively long half life of 244 days of  $^{67}\text{Zn}$  make this isotope less suitable for autoradiographic studies *in vivo* in man.

TAYLOR (1957) reported that slices of tissues incubated with  $^{67}\text{Zn}$  *in vitro* will take up the isotope in concentrations corresponding to those obtained after its injection into the intact animal. This *in vitro* technique appeared to be a suitable one with which to study the localization of  $^{67}\text{Zn}$  incubated in the testes and epididymes in man.

*Material and Methods:* The testes and the epididymes were obtained from three patients subjected to unilateral or bilateral removal of the scrotal contents.

The unilateral operation was carried out on a 68-year-old man with a recurrent scrotal hydrocele and on whom hydrocelectomy had earlier been performed. The bilateral operations were performed on two elderly men, aged 72 and 78, with carcinoma of the prostate. Both subjects had been treated with an oestrogen, aethinylloestradiolum, 0.15 mg daily. The first man received oestrogen at short intervals over 9 months, about a year later operation was undertaken because the patient refused to continue the oestrogen treatment regularly. The 78-year-old man received oestrogen for only two weeks when the therapy had to be abandoned because of allergic reactions; operation was performed 4 months later. The two subjects were in good general condition without clinical and roentgenologic signs of metastases.

The original radioactive zinc,  $^{67}\text{Zn}$ , was obtained from the Biochemical Centre, Amersham, England, as a  $^{67}\text{ZnCl}_2$  solution. The original isotope solution was diluted with 0.85% sodium chloride to a final solution of 40  $\mu\text{Ci/ml}$  specific activity and a pH of 6.5 in which the organs to be studied were immersed.

Small 4 to 8 mm cubes were cut out from the testes and the epididymes and incubated in the radioactive solution for two hours at  $\pm 37^\circ\text{C}$ . The tissues were fixed in formalin and processed by standard methods, 5 to 8  $\mu$  serial

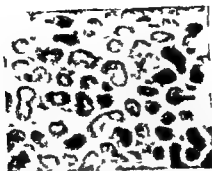


Fig 1 Autoradiograph from the testis of a 68 year-old man after incubation with  $\text{Zn}$  in vitro. Blackened areas indicate high concentrations of radioactivity  $\times 30$

sections were cut and every second one was mounted on glass and the others on methacrylate slides, the former being stained with hematoxylin and eosin.

The methacrylate slides were subjected to autoradiography. Agfa Printon Rapid films were used and the apposition technique and the exposure of the films were carried out in accordance with the method described by ODEBLAD (1952). An appropriate blackening of the films was obtained after an exposure time of 4 months. The films were developed in Gierert 209 A at 20 to 22° C and fixed in Gierert Acido Fix.

### Results

Autoradiographs of the testis and of the epididymus are presented in Figs 1 and 2. The concentration of  $^{65}\text{Zn}$  is indicated by blackening in the reproductions.

The concentration of radioactive zinc showed a characteristic and uniform pattern with a various degree of uptake in the different tissue elements in all the areas examined. The peripheral parts of the tissues presented no visible increase in radioactivity compared to the central parts.

The germinal cells in the testes and the epithelium cells lining the epididymal ducts showed evidence of a relatively high concentration of radioactive zinc compared to the interstitial tissues in these areas. The contents of the seminiferous tubules of the testes also displayed a high concentration of radioactive zinc (Fig 1). The degree of radioactive uptake seemed to be closely related to the amount of contents in the ducts. Where microscopic investigation revealed large amounts of ductal contents the blackening was comparatively greater than where the amounts were small. The contents of the ducts in view of their relatively low tissue density, had a high uptake of radioactive zinc. The contents are formed by products from the testes.



Fig 2 Autoradiograph from the epididymus of a 72 year old man after incubation with  $^{65}\text{Zn}$ . Blackened areas indicate high concentrations of radioactivity  $\times 30$

A peripheral zone of faint blackening encircling the ductal contents was seen in both the testes and the epididymes. This was probably an artefact due to a shrinkage effect of the tissues during the histologic fixation. The interstitial tissues of the epididymes as well as those in the testes displayed a relatively low degree of blackening. A high concentration of radioactive zinc occurred in the small blood vessels in both organs.

### Discussion

Autoradiographs of the testes and the epididymes in man using radioactive zinc  $^{65}\text{Zn}$  do not appear to have been presented earlier.

The uniform and characteristic distribution of the radioactive zinc in the different sections studied was noteworthy and appeared to offer a possibility of studying the distribution of zinc in the different tissue elements of the testes and epididymes. The various parts of the organs are believed to take up  $^{65}\text{Zn}$  in amounts corresponding to those of the natural occurring zinc during the two hours incubation in the radioactive zinc solution. Metabolic events such as the transport of zinc through the epididymal ducts by products from the testes will naturally not be illustrated by this method, and experiments such as those carried out in rats by WETTERDAL (1958) and by MILLAR, VINCENT & MAWSON (1961) would appear to be necessary for studies *in vivo*. Similar experiments in man are at present unsuitable for reasons already mentioned.

Unfortunately we had to study organs from elderly subjects since the removal of clinically normal scrotal contents is only exceptionally carried out in others. The microscopic investigations revealed satisfactory spermiogenesis with epididymal ducts packed with spermatozoa and otherwise normal appearances. The testes and the epididymes of these elderly men were thus considered suitable for use in the studies intended.

The autoradiographs disclosed some interesting facts. A relatively high amount of radioactive zinc was evident in the germinal cells and in the contents of the seminiferous tubules of the testes. Earlier observations in rats by WETTERDAL (1958) and MILLAR VINCENT & MAWSON (1961) indicated that radioactive zinc is incorporated slowly into the testicular spermatozoa. The present autoradiographs revealed high concentrations of radioactive zinc in the contents of the seminiferous tubules. It may be that the spermatozoa in man during their development in the seminiferous tubules gradually increase their supplies of zinc. The high concentration of radioactive zinc in the germinal cells indicate that these cells are the source of the zinc that will be delivered to the spermatozoa. part of the zinc accumulated in the tubules is probably attached to the seminal plasma.

The epithelium cells lining the ducts in both the caput and the cauda epididymidis showed a similar and relatively high concentration of radioactive zinc. Metabolic events such as the gradual progress of radioactive contents through the epididymal ducts will not be reproduced by the present in vitro method.

The high concentration of radioactive zinc in the epithelium cells compared to the relatively weak concentration in corresponding cells in rats 13 days after an intraperitoneal injection of  $^{65}\text{Zn}$  (MILLAR VINCENT & MAWSON 1961) was an observation considered to be of importance. BIRNBAUM, HALL & LEE (1961) studied the zinc content of the sperm cells of the testes, epididymes and vas in rats and their results suggested an increasing zinc content by the processing of the spermatozoa. It may perhaps be presumed that the spermatozoa during their development in the sperm transport system receive further zinc in the epididymal ducts.

The zinc is also attached to the seminal plasma. EABON & WETTERDAL (1961) using paper electrophoresis studied the distribution of  $^{65}\text{Zn}$  added in vitro to human semen. The isotope was found to migrate together with a protein component supposed to be a beta globulin appearing in both fertile and in fertile ejaculates. This protein bound zinc could not be shown to be significantly influenced by the number or the morphology of the spermatozoa.

### Acknowledgement

The investigation was supported by a grant from Stiftelsen Thérèse och Johan Anderssons Minne.

### SUMMARY

The testes and the epididymes of three human subjects were incubated with  $^{65}\text{Zn}$  in vitro. The distribution of the isotope within the different tissues was studied by an autoradiographic technique.

## ZUSAMMENFASSUNG

Die Testes und die Epididymes von drei Fällen wurden mit  $^{65}\text{Zn}$  *in vitro* inkubiert. Die Verteilung des Isotops in den verschiedenen Organen wurde mit Hilfe einer autoradiographischen Technik studiert.

## RÉSUMÉ

Les auteurs ont incubé les testicules et les épидидymes de trois sujets humains avec du  $^{65}\text{Zn}$  *in vitro*. Ils ont étudié la distribution de cet isotope dans les différents tissus par une technique autoradiographique.

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## AUTOMATIC ISODOSE RECORDER

by

INGEMAR LARSSON, KURT LIDEN and NILS STARFELT

In modern radiotherapeutic planning a detailed and accurate knowledge of the radiation field to be used is very important. In practice a determination of sets of isodose curves in one or several planes will give the necessary basic information and for such purposes automatic isodose plotters are invaluable. Such devices have been described by KEMP (1946), HINE, BERMAN and ELKIND (1950), MAUCHEL and JOHNS (1954), SIMONS (1956). KEMP compared the step by step integrated dosage rates of two ionization chambers, the exploring chamber moving in a cartesian system. HINE et al. (1950) described a device with a scintillation crystal by means of which the 'isocount' curves around a  $\gamma$  emitting source rotating on a turntable could be recorded. The plotters described by MAUCHEL and JOHNS and by SIMONS compared two dosage rates from ion chambers. The former authors placed the moving chamber in a vertical polar system and the latter author used a vertical cartesian system.

The plotter developed by the present writers compares the dosage rates from two organic scintillators, the exploring scintillator moving in a horizontal polar system. The machine has now been successfully operated over a period of five years (LIDEN 1957). Investigations of the isodose curves of roentgen



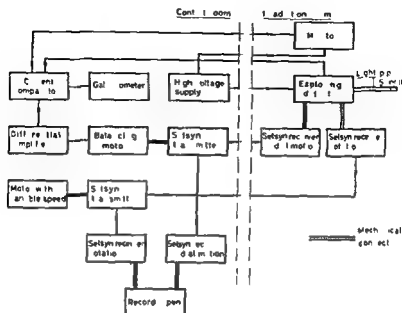


Fig 1 Block diagram of the isodose recorder

and cobalt beams, as well as of radium and tantalum applicators, have been performed

*Design of the isodose recorder* As an exploring detector the present isodose recorder utilizes a scintillator which is restricted to move in a system of polar coordinates. The principle of operation is shown in Fig 1. Photographs of the actual apparatus are reproduced in Fig 2. The isodose recorder consists of two separate horizontal arms which are given a synchronous rotational motion around a vertical axis by means of a reversible motor and a Selsyn system. These arms are supplied with radially movable carriages both of which are connected to the balancing motor through a Selsyn system. One of these carriages carries the exploring dose detector and the other one a pen which continuously reproduces the motion of the exploring detector on a sheet of paper. The mechanical mounting of the arms made of stainless steel tubes and the location of the carriages for detector and pen, are displayed in Fig 2. The origin of each polar coordinate system is adjustable. The reason for this will be explained later. The carriages can be moved about 50 cm in the radial direction by means of a steel wire and gear arrangement.

Light from the irradiated scintillator is transmitted through a light pipe to a RCA 1P21 photomultiplier. The anode current from this photomultiplier is compared in a comparator circuit with the current from another photomultiplier receiving the light from a scintillator which is also irradiated by the source under investigation. This monitor is mounted in a fixed position care

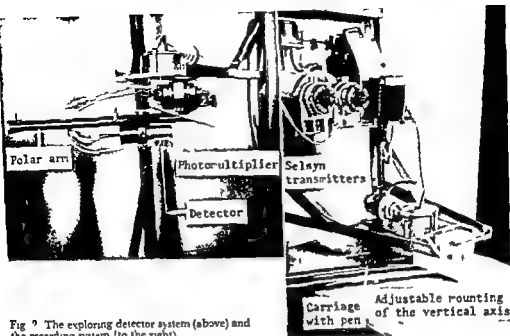


Fig 2 The exploring detector system (above) and the recording system (to the right)

being taken to ensure that the exploring detector never interferes with the radiation impinging on the monitor. The variations in output from certain radiation sources necessitates the use of a monitor instead of a constant current source. The monitor detector follows the variations in output and so does the exploring detector current. Therefore small variations in output will not influence the curve being recorded.

When the rotational motion tends to carry the exploring detector along a path which is not an isodose curve, the balance in the comparator circuit is disturbed. An error signal is given to a differential amplifier and the balancing motor controlling the radial motion drives the exploring detector back to the isodose curve. Thus the balance is restored and the exploring detector is forced to stay on the predetermined isodose curve. This curve is recorded on a sheet of paper by the pen on the other carriage. By using sufficiently long cables the exploring detector system can be mounted in the irradiation room and the recording and driving components in a shielded room.

The current comparator circuit is shown in Fig 3. The galvanometer with an internal resistance of  $5\text{ k}\Omega$  can be used to measure the current in each of the two branches. It has a sensitivity of  $5 \cdot 10^{-10}\text{ A}$  per division. The dark current through the resistors  $R_2 + R_3$  is balanced out by applying a certain voltage from battery B.

The circuit is in equilibrium when the position of the exploring detector

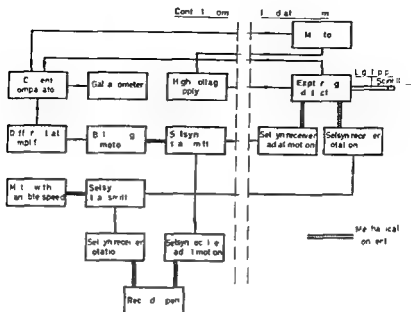


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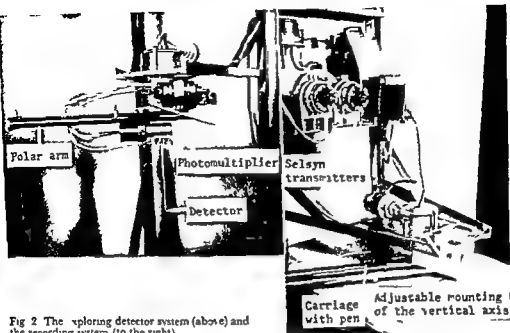


Fig 2 The exploring detector system (above) and the recording system (to the right)

being taken to ensure that the exploring detector never interferes with the radiation impinging on the monitor. The variations in output from certain radiation sources necessitates the use of a monitor instead of a constant current source. The monitor detector follows the variations in output and so does the exploring detector current. Therefore small variations in output will not influence the curve being recorded.

When the rotational motion tends to carry the exploring detector along a path which is not an isodose curve, the balance in the comparator circuit is disturbed, an error signal is given to a differential amplifier, and the balancing motor controlling the radial motion drives the exploring detector back to the isodose curve. Thus the balance is restored and the exploring detector is forced to stay on the predetermined isodose curve. This curve is recorded on a sheet of paper by the pen on the other carriage. By using sufficiently long cables the exploring detector system can be mounted in the irradiation room and the recording and driving components in a shielded room.

The current comparator circuit is shown in Fig 3. The galvanometer with an internal resistance of  $5\text{ k}\Omega$  can be used to measure the current in each of the two branches. It has a sensitivity of  $5 \times 10^{-10}\text{ A}$  per division. The dark current through the resistors  $R_1 + R_2$  is balanced out by applying a certain voltage from battery B.

The circuit is in equilibrium when the position of the exploring detector

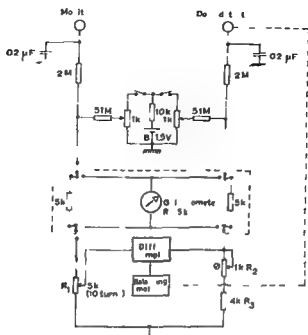


Fig 3 Current comparator circuit

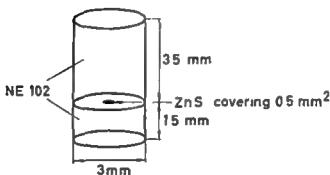


Fig 4 Compound scintillator

in the radiation field is such that the currents through the resistors  $R_1$  and  $R_2 + R_3$  keep the two inputs of the differential amplifier at the same voltage

The exploring detector should be able to measure small doses in roentgen units and should be small in size in order to permit a detailed study of the radiation field close to the source. The detector should moreover be made of a material having a density and atomic number close to that of tissue or water in order not to disturb the radiation field under investigation. In order to ensure a satisfactory operation of the differential amplifier it is important that the detector currents be sufficiently strong.

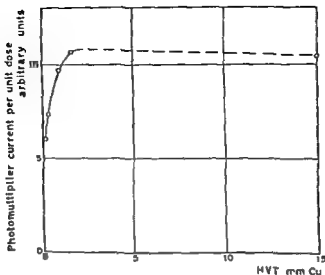


Fig 5 The dependence of the dose response on radiation quality for an anthracene crystal (diam 3 mm length 3 mm)

The light from the scintillator can most efficiently be transmitted to the photomultiplier by means of a light guide of quartz or lucite. However, in this case a disturbing background may arise from Cerenkov light generated by Compton electrons in the light guide. This has also been pointed out by BELCHER (1953), SHALEK and COLF (1958). In an early design two identical light guides and photomultipliers were mounted side by side but only one was supplied with a scintillator. The difference between the currents from the two photomultipliers then represented the light from the scintillator itself. However this arrangement requires that the photomultipliers be exactly adjusted to give the same sensitivity and that the light guiding rods be equal in performance. It was found that internally polished dural tubes are quite efficient light pipes and such tubes were then used.

A cylindric scintillator with a diameter of a few millimeters mounted at the end of a light pipe 20 to 50 cm in length in conjunction with a photomultiplier having a high sensitivity and low dark current fulfills all of the above requirements.

Measurement in  $r$  units implies that the scintillator should always emit the same amount of light at a certain dose rate irrespective of the spectral composition of the radiation. Therefore a review of the roentgen ray and  $\gamma$  ray spectra of interest should be made. In the case of a  $\text{Co}^{60}$  source the radiation close to the source consists of primary  $\gamma$  rays 1.17 and 1.33 MeV. With increasing depth in water the relative amount of degraded radiation increases. For roentgen ray spectra from roentgen generators the situation is similar but here the degraded photons dominate at much smaller depths.

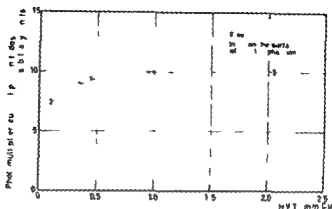


Fig. 6 The dependence of the dose response on radiation quality for the compound scintillator of fig. 4

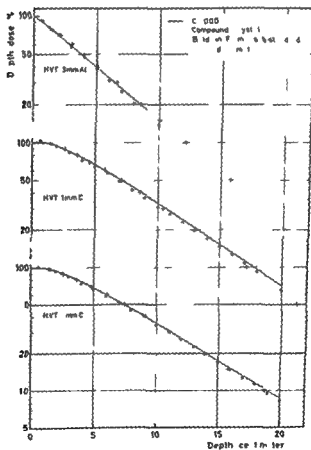


Fig. 7 Comparison between measured depth dose data (+ and ) and values obtained from Central Axis Depth Dose Data (1953) (solid line)

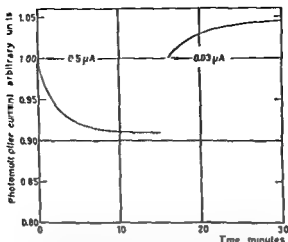


Fig 3 Photomultiplier fatigue effect At zero time the detector is placed in a radiation field giving rise to a photomultiplier current of  $0.50 \mu\text{A}$ . The detector is irradiated with constant intensity for 15 min and then moved to a point where the radiation field gives rise to a photomultiplier current of  $0.030 \mu\text{A}$ .

For  $\text{Co}^{60}$  anthracene crystals can be used. For radiation of lower energy special compound crystals are needed (RAMM 1956). Combinations of a plastic scintillator and  $\text{CaWO}_4$ ,  $\text{NaI}$  or  $\text{ZnS}$  have been investigated. The best results have been obtained with a scintillator, 3 mm in diameter, consisting of two pieces of solid Ne 102 plastic scintillator (Nuclear Enterprises Ltd, Edinburgh) sandwiching a very small amount of  $\text{ZnS}$  powder (Fig 4) which were heated up in an oven and pressed together. The light output from this scintillator was 67 % of that obtained from an anthracene crystal  $3 \times 3$  mm at a roentgen radiation quality of 2 mm Cu HVT. The different scintillators were tested in two ways. The first method involved a comparison with a simultaneously irradiated standard ion chamber both in air and on the surface of a water phantom with roentgen rays of different qualities and with a radium source (Figs 5 and 6). The relative depth dose in a water phantom for a series of primary radiations was also compared with depth doses measured by means of a Baldwin Farmer substandard roentgen ray dosimeter and with data from depth dose tables (Fig 7). The first method shows that the compound scintillator is superior to the anthracene scintillator at low energies. From the second test (Fig 7) it is obvious that this scintillator can be used down to fairly great depths even with primary roentgen rays of low energy.

*The photomultiplier gives rise to the following difficulties*

- 1 In many cases the direct radiation from the source that strikes the photocathode and the dynodes results in a current which is not small compared to



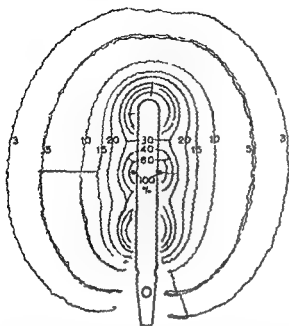


Fig. 9 The system of isodose curves around a 150 mC radium applicator in a water phantom. The 100% point is located 1 mm from the surface of the applicator. Anthracene crystals of 1.5 and 3.5 mm diameter were used. The 5% curve is recorded with both crystals.

the current caused by the light from the scintillator. Because the detector has to be easily movable to give a fast response to a small change in dose rate it is often difficult to shield the photomultiplier sufficiently with lead. Therefore the light pipe is made as long as is convenient and a remotely controlled shutter is placed in the light pipe close to the photomultiplier so that the current from the direct irradiation of the photomultiplier can be measured at any time and compensated for electrically in the same way as for the dark current.

2 To make it possible to measure low intensity radiation with small crystals and long light pipes the dark current from the photomultiplier has to be extremely low and constant. Selected 1P 21 tubes have been used but at high relative air humidity the dark current has often been excessive. A cut in the tube socket to increase the distance along the surface of the insulating material between the anode and the cathode was found to be helpful. But nevertheless it is necessary to compensate for the dark current.

3 The third difficulty is due to the fatigue effect of the photomultiplier, as demonstrated by Fig. 11. It can be seen that the current approaches its steady value asymptotically. It is therefore in most cases sufficient to wait two or three minutes after placing the detector in the appropriate radiation intensity before running through an isodose curve.

**Operation** The recording of an isodose diagram is performed in the following way. The exploring detector is placed at a point to which a certain percentage dose is ascribed from earlier measurement or by definition, for example 100% at the surface of a phantom. A high voltage is used giving a current of about

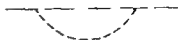
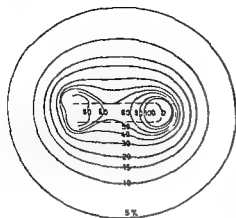


Fig 10 Isodose curves around a tantalum wire shaped as a bent hair pin. The tantalum wire is shown as a line of dashes. The dots and dash line in the right hand part of the figure is the plane of observation. The 100 curve corresponds to 3 l r/hr per mC.

2  $10^{-7}$  A from the exploring detector. For this current the fatigue effect is low and when recording at lower dose rates a change in the abovementioned current of about one per cent will give rise to a signal that is strong enough to operate the differential amplifier, thus affecting the balancing motor. The dark current from the two photomultipliers is then measured with the radiation source removed and compensated for by means of the battery (see Fig 3). The battery is also used to eliminate the background current from the exploring detector caused by the source as measured with the shutter closed in the light pipe. With the potentiometer  $R_1$  adjusted to read the abovementioned dose rate the monitor detector is moved or its high voltage is changed until the comparator is balanced, i.e. until there is no output from the differential amplifier. These operations are performed before the motors are connected to the transmitters of the Selsyn system. After connecting the motors the exploring detector proceeds along the desired isodose curve.  $R_1$  is then adjusted to a new value. The detector is left on the new isodose curve 2 to 3 minutes with the motors disconnected to allow for the fatigue effect in the photomultiplier. If necessary the comparator is then rebalanced and a new isodose curve is recorded.

It is often convenient to use two or more scintillators of different sizes when recording a set of isodose curves. Close to the radiation source, where the dose rate is high, the best possible geometric resolution is desired and thus a small crystal should be used. Far away from the source the isodose curves are usually well separated from one another and the accuracy can then be improved by increasing the signal through the use of a larger scintillator. It may also be necessary to increase the high voltage when recording at low dose rates in order to get a sufficiently large signal. As mentioned above it is the radial motion of the detector system that is influenced by the dose rate in such a way that

the detector stays on an isodose curve when the rotational motion proceeds at constant speed. It is then convenient to locate the center of rotation in such a position that the dose rate decreases with increasing distance from this center for all points of the isodose curve to be recorded. Otherwise the polarity of the signal to the differential amplifier has to be reversed at certain points on the isodose curve. In certain cases it may be necessary to record a system of isodose curves in two or more separate runs, moving the detector coordinate system to a new position in between consecutive runs (cf Fig 10). It is for this reason that the two coordinate systems are made adjustable (Fig 2).

### Discussion

The performance and accuracy of the isodose recorder can best be illustrated by discussing the systems of isodose curves obtained with some specific radiation sources. Fig 9 shows a clean copy of the system of isodose curves obtained with a 150 mC Ra applicator in a water phantom. The 100 % point was registered with a scintillator 1.5 mm in diameter in a 2 mm diameter container. Thus this point is located only 1 mm from the surface of the applicator. The 5 % curve was recorded twice using two different scintillators, the one just mentioned and a larger one with a diameter of 3.5 mm. All curves corresponding to a dose rate higher than 5 % were run with the small detector and the 3 % curve with the large one.

Bladder tumours are sometimes treated with the radiation from implanted radioactive tantalum wires, Ta<sup>182</sup>. A wire in the form of a somewhat bent hair pin is implanted in the wall of the bladder by means of a special instrument. The dose delivered in this treatment was earlier determined only by theoretical calculation. The accuracy of treatment planning has been considerably

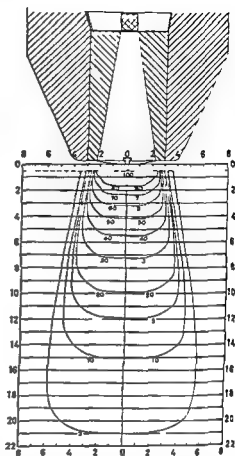


Fig 11 The system of isodose curves for a 20 curie Co unit in a water phantom. FSD 10 cm, field size 4.5 cm by 3.0 cm. The central axis is in the plane of the diagram, the 4.5 cm side of the field is parallel to this plane. The 100 % point is located at a point 0.5 cm below the surface of the phantom. Anthracene crystals having diameters of 3.5 and 5.5 mm were used.

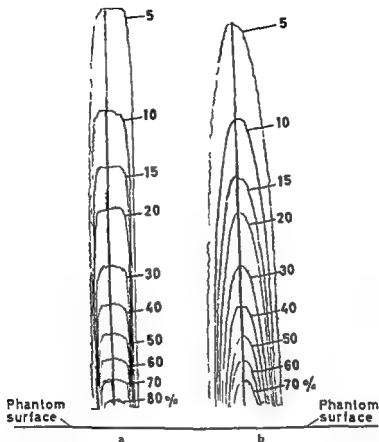


Fig 12 Isodose curves with narrow beams of roentgen rays with 40 cm FSD and 1 mm Cu HVT with a 1 cm diaphragm on the surface of the phantom (a) and with the diaphragm located 27 cm from the focus (b) giving a geometric field of 1 cm on the phantom surface. The position of the 70 point on the central axis was determined from zero-field data tabulated in Central Axis Depth Dose Data (1953). A compound scintillator was used (dimensions: diam 3 mm, length 4 mm).

improved by using recorded systems of isodose curves in different planes around both straight and bent tantalum needles in a water phantom (Fig 10). Absolute determination of the dose rate has been made by means of micro-ionization chambers (SIEVERT 1934, SKOLDBORN 1959) calibrated with a standard radium source. The 20 curie  $\text{Co}^{60}$  unit in Lund, which was used for treatment at a FSD up to 10 cm, was equipped with collimators for rectangular fields. The radiation field obtained with these collimators was studied with the isodose recorder. Systems of isodose curves were recorded in different planes. As an example of the results of these measurements, the isodose curves in a plane through the axis of the collimator and parallel to the longest side of

the rectangular field is shown in Fig 11 The 100 % point was located at a depth of 0.5 cm below the surface of the phantom

The last example is chosen in order to illustrate the effect on the dose distribution of the position of the diaphragm when using a narrow beam from a roentgen tube having a 1.2 cm focus (Fig 12)

Finally it should be mentioned that for all the cases now discussed dose rate (e.g. r/hr or r/min) can be ascribed to the isodose curves registered This may be done either by absolute calibration of the detector or by determining the dose rate by means of an ionization chamber at one point on an arbitrarily chosen isodose curve

### Acknowledgements

The authors are greatly indebted to Dr J. Cederlund for valuable assistance The investigation was supported by grants from the Swedish Cancer Society

### SUMMARY

The design and operation of an automatic isodose recorder is described The recorder compares the electric currents produced by the simultaneously irradiated monitor and exploring probe the latter being restricted to move in a system of polar coordinates The probe consists of a small exchangeable organic or compound scintillator 1 to 6 mm in diameter connected to a RCA 1P21 photomultiplier through a light transmitting tube Systems of recorded isodose curves for radium and Ta 182 applicators and for roentgen and  $\text{Co}^{60}$  beams are shown indicating good reliability and flexibility of the equipment

### ZUSAMMENFASSUNG

Die Konstruktionen und die Funktion eines automatischen Isodosenschreibers werden beschrieben Der Schreiber vergleicht die elektrischen Ströme die in einem stationären Monitor und in einem beweglichen Detektor produziert werden die Bewegung des letzteren geschieht in einem polaren Koordinatensystem Der bewegliche Detektor besteht aus einem kleinen auswechselbaren organischen oder kombinierten Szintillator 1 bis 6 mm in Diameter der durch einen Lichtleiter an einen RCA 1P21 Sekundärelektronenervielfacher angeschlossen ist Diejenige Systeme von Isodosenkurven die für Radium und Ta 182 Applikatoren und für Röntgen- und  $\text{Co}^{60}$  Strahlung registriert sind zeigen dass die Apparatur zuverlässig und vielfach verwendbar ist

### RÉSUMÉ

Les auteurs décrivent la construction et le fonctionnement d'un inscripteur automatique de courbes isodoses L'inscripteur compare les courants électriques produits par le monitor et une sonde exploratrice irradiés simultanément la sonde étant astreinte à se déplacer dans un système de coordonnées polaires La sonde est faite d'un petit scintillateur organique ou composé interchangeable d'un à six millimètres de diamètre relié à un photomultiplicateur RCA 1P21 par un tube transmetteur de lumière Les auteurs présentent des systèmes de courbes isodoses enregistrées avec cet appareil pour des applicateurs de radium et de Ta 182 et pour des rayonnements roentgen et du  $\text{Co}^{60}$  ces courbes montrent la fidélité et la maniabilité de cet appareil

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## ROLE OF TRAUMA IN THE DEVELOPMENT OF MALIGNANT BONE TUMOURS

by

CARL KREBS and KAJ OLSEN

It has been established that exposure to radiation and to chemical, thermic and hormonal stimuli may have a cancerogenic effect (2, 3) and that chronic infection may occasionally be complicated by neoplastic changes (12). Under experimental conditions the latent period for the development of transplantable tumours is apparently shortened when the animals are exposed to repeated surgical trauma (5) although tumours have scarcely ever been induced without the contributory action of co carcinogens (8, 10). A few authors state however, that this may occur in rare cases (11).

The cancerogenic importance of traumatic injury in the development of malignant tumours mentioned in the older textbooks (1, 14) presumably arose from the patients' statements that a definite injury provoked the malignant condition.

The numerous major and minor injuries of everyday life may readily be forgotten but a certain incident will more easily be remembered if a pathologic change that was not noticed although perhaps present at the time of the injury became evident shortly afterwards. There are certain other factors that are relevant. A tumour bearing limb will often go unnoticed by the patient, be slightly asynergic and thus be more liable to injury. The limb is often hypersensitive, so that even slight injury may produce relatively severe pain or tenderness. It

might also be mentioned that modern insurance conditions may influence the patient's attitude since his financial position will be more favourable after an accident than he would be with other conditions. Long term observations (5, 6) of patients who during World War I were exposed to severe trauma showed an incidence of malignancy in the order of one in 700. An analysis of this large series revealed no obvious increase in morbidity as compared with corresponding groups of the general population.

POULSEN (13), in a review of the files of the Directorate of Accident Insurance in Denmark for the years 1931—1940, found 86 cases with the diagnosis of cancer, including 29 accepted as caused or aggravated by traumatic injury. The records of the Radium Centre of Copenhagen for the same period recorded a history of trauma in 14 of 40 cases of bone tumours. A critical reappraisal of these two series shows, however, that in only one case of each series is it impossible to rule out that the disease had been caused by the injury. The tumours occurred in the age groups in which the highest cancer incidence is generally found.

An analysis of 168 cases of malignant bone tumours was as follows:

Clinical notes	1931—1949	1950—1959
Trauma sustained	28	33
Pathologic fracture	8	6
No trauma	52	43
No information as to trauma	6	6

The results of reappraisals of previous roentgenograms in four cases are reported below. The subjects were assumed to be in good health at the time when the trauma was sustained. The pathologic changes present were missed at the first roentgen examination, the presence of a tumour not being revealed until after the lapse of several months. If the original films had not been available, the case history would have indicated that the new growth was caused by the injury. In addition, a fifth case illustrates how metastases may select a site where traumatic injury has been sustained.

*Case 1* Man, aged 21, who sprained his right ankle during military service (Fig. 1a). The ankle was put in plaster and three control roentgen examinations were performed.

Four months after the injury, an osteogenic sarcoma became apparent at the site and metastases were found in the lungs. The patient was eventually admitted to the Radium Centre (Fig. 1b). Death occurred 3 years later.

*Case 2* Boy, aged 13, who sustained a fracture of the left humerus in a fall (Fig. 2a). Uncomplicated union with complete restoration of function occurred after immobilisation. Four months later a swelling of the shoulder was noticed and an osteogenic sarcoma was diagnosed (Fig. 2b). Death ensued 17 months after the injury.

*Case 3* Boy, aged 16, sustained a transverse fracture of the femur while playing football (Fig. 3a). He was treated with extension and three and a half months later could walk with





Fig 1 Case 1 *Left* A-p and lateral views following trauma. Superficial destruction with spicule formation at the posterior aspect of the distal part of the tibia. *Right* 7 months later. Tumour with separation of the syndesmosis

the support of a stick. A further fracture occurred at the same site six months after the trauma and a bone tumour was then detected. Biopsy was not performed. The patient is still alive (Fig 3b).

*Case 4* Boy, aged 3 years, was examined because of a minor trauma to the right shoulder; no evidence of fracture. Four months later swelling of the right upper arm occurred and a Ewing sarcoma involving the entire diaphysis was apparent. Death ensued 14 months after the accident. Re-appraisal of the first films showed fine periosteal thickening 10 cm in length of the shaft of the humerus — signs of the incipient tumour.

*Case 5* Man, aged 35, noticed a swelling of the right eighth rib and thought that it had been caused by an injury sustained two years previously. Clinical examination revealed a Ewing sarcoma of the rib which subsided after roentgen therapy, and the rib was resected three months after the commencement of the treatment.



Fig 2 a) Spiral fracture of the humerus with an area of destruction in the neck due to an osteogenic sarcoma b) Four months later

The patient later stated that he had had a lump on his scalp for some months. Roentgen examination of the skull revealed bone destruction at the site of the tumour; all the changes rapidly disappeared following roentgen irradiation. The patient died with extensive metastases 33 months after the first admission. It is probable that the lesion of the rib was actually a metastasis situated in a locus minoris resistentiae that had occurred after the trauma and that the primary growth was in the calvarium.

### Discussion

A deep seated (or merely subcutaneous) tumour is not likely to be palpable until it consists of at least  $10^8$  tumour cells (weighing less than 1 g). The minimum time of generation for cell division is about 20 hours under experimental conditions in tissue culture and there is nothing to suggest that the growth rate is higher in vivo. On the assumption that the time of generation is 24 hours and that no cells die but all contribute to the expansion of the tumour  $10^8$



Fig 3 a) Malignant destruction around the site of fracture b) and c) Six months later The changes have advanced

cells will have developed after 10 days  $10^4$  in three weeks and  $10^8$  within a month

Assuming that a normal cell may become malignant after exposure to trauma a tumour induced in this way can arise from only one or a few cells The growth rate of bone tumours at the time of diagnosis is fairly well known — a tumour does not double in size from day to day It is therefore improbable that extremely rapid growth occurs in the earliest stages of the development of a tumour Several cells may of course simultaneously participate in the development of a tumour but some months will presumably be required before it attains a palpable size Accordingly if a bone tumour is diagnosed earlier there is every probability that it existed at the time when the trauma was sustained

An incipient tumour as already mentioned may very well consist of  $10^4$  cells or more without being detectable If such a tumour is exposed to mechanical trauma its capsule may rupture and massive spread occur due to (1) liberation of malignant cells by the injury (2) vascularisation before and during the re absorption of a haematoma (3) more portals for metastases are created, (3) the pressure within the tissue and hence the tendency to metastases being increased by extravasation

Reparative processes with or without inflammation constitute a stress on the normal resistance of an organism and surgical procedures may possibly have a similar effect

It is known that tumour cells are constantly circulating in the blood stream in cases of malignancy. The host organism is, to an appreciable extent, capable of destroying such cells, so that the development of metastases occurs only in exceptional cases during the early stages of the disease (9). After exposure to trauma, much of the physiologic reserve may be expended in reparative processes and favourable conditions for the development of secondaries created at the site of the contusion (10), and in this fertile soil a secondary tumour may develop (Case 5).

Theoretical considerations would thus appear to be against the assumption of a causal relationship between trauma and the development of neoplasms. Injury may aggravate an existing neoplasm, but this may be an advantage in that the patient may seek aid earlier than he would otherwise have done (traumatic determinism).

The case histories reported confirm Ewing's words: 'Trauma reveals more malignant growth than it produces' (4).

## SUMMARY

The possible significance of trauma in producing or aggravating malignant bone tumours is discussed.

## ZUSAMMENFASSUNG

Der mögliche Einfluss von Trauma auf die Entstehung und Verschlimmerung von malignen Geschwulsten wird diskutiert.

## RÉSUMÉ

Les auteurs étudient l'influence possible des traumatismes sur l'apparition ou l'aggravation des tumeurs osseuses malignes.

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## LEUCOCYTE MIGRATION IN PARTIAL BODY IRRADIATION OF GUINEA PIGS

by

B TRIBUKAIT A FORSSBERG and CHRISTINA ÖSTERDAHL

White cells are extremely motile and may readily be caused to migrate from the blood circulation to depot tissues such as the bone marrow or capillary beds (Cf Ciba Foundation Symposium on Haemopoiesis London 1960 and DOUGHERTY 1952) Whole body irradiation of animals causes within the first few hours an increase of leucocytes except of lymphocytes in the circulation (HULSE 1960) a reaction which is due to a release of cells from depot tissues This is a transient stage and within a few hours it is followed by a general decrease, the well known effect in radiation work The initial rapid concentration changes are in themselves of interest, however as an indication of early changes produced by irradiation

The complexity of these phenomena was discussed in a previous publication (FORSSBERG, TRIBUKAIT & VIKTERLOF 1961) An increase in some leucocyte groups and a fall in others were observed reactions that were clearly dose dependent Species differences between guinea pigs and mice were also noted

It is demonstrated in the present investigation that partial body irradiation even of relatively small areas may initiate specific reactions of segmented cells and lymphocytes that have been forced into the blood circulation The studies were confined to guinea pigs as these animals are best suited to such procedures and are also more radiation sensitive

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*Material and Methods* The guinea pigs were of the same origin as previously used, the average weight of the animals at the time of the irradiation was in all series, excepting one, about 175 to 225 g. In one series 400 g animals were used but this weight increase caused no difference in the reactions. The irradiations were given under the same running conditions as previously: 250 kV, 15 mA, HVL 1.6 mm Cu, dose rate 110 rad/min, as measured on the surface of the irradiation fields. The whole body irradiations were in our previous studies given in three sets, over the left and right flanks and over the dorsal side. As this was not possible in the partial body program, all irradiations, even the whole body doses, were given in one delivery. The rest of the animal was lead shielded in the partial body irradiations. Comparison was made between irradiations of small abdominal fields as specified on p. 52, and whole body irradiations. In both procedures the beam was directed towards the abdomen and the doses were given under ether anaesthesia. Simultaneously, control groups of normal but sham treated, as well as anaesthetized and sham treated animals, were run. We had to confine our observations to the effects at one dose level, 300 rad, and at a single time of four hours after irradiation at which time it had previously been found, the effects are well expressed.

The evaluation of the results was based entirely on the two large groups of segmented cells and lymphocyte cells although differential counts on all the white cell groups were made. The rods and monocytes mainly followed the segmented cells in their reaction pattern but in this limited material the numbers were too small for statistical treatment. The previous work should be consulted for other experimental details.

## Results

Several sets of experiments from a general survey to a more detailed analysis in a particular case, were performed.

The control group (1) and the whole body irradiation group (2) were in the first series compared with groups of animals which had received irradiation as follows: (3) the head including the upper part of the shoulders; (4) the middle part including the lungs and abdomen; and (5) the hind quarters up to and including the hips. A further group (6) in which the intestines and the greater part of the lungs were lead shielded while the head and hind quarters received irradiation, was also compared. This latter group was selected to be approximately equal to the middle part (group 4) in regard to body volume. All doses were given from the dorsal side. Anaesthesia was not necessary in these experiments since the animals remained quiet in the irradiation cages. The data are presented in Table 1 (series I).

An increase of segmented cells occurred in all the groups but there is no clear relationship between the percentage of the irradiated body volume and that of the released cells. Although the head and hind part are each by volume

Table 1

*Series I Whole body and partial body irradiation of groups of guinea pigs 10 animals in each group The number of segmented cells and lymphocytes per mm<sup>3</sup> in the blood 4 hours after 300 r irradiation and the percentage concentration is given*

*Series II Left side and right side irradiation similar data as in series I Two sets of experiments with 10 animals in each group*

Series	Group	Approximate irrad	Segmented		Lymphocytes	
			n	%	n	%
I	(1) controls irrad of	—	654 ± 138	16.4	3167 ± 347	81.5
	(2) whole body	100	2430 ± 495	42.5	2414 ± 516	45.7
	(3) head	70	1663 ± 367	31.1	3107 ± 403	63.7
	(4) middle part	60	2977 ± 580	47.3	2506 ± 395	41.7
	(5) hind	20	1661 ± 283	32.3	3195 ± 416	61.9
	(6) head + hind	65	2748 ± 457	34.6	4559 ± 800	58.4
II	(1) left side	50	1973 ± 479	25.1	5533 ± 930	70.8
	(2) " "		1922 ± 393	24.7	5424 ± 470	70.6
	(1) right side	50	4669 ± 895	41.3	5971 ± 1006	53.4
	(2) " "		2966 ± 341	39.7	4077 ± 416	53.9

weight not more than about 20 % of the total weight of the whole body, the figures for segmented cells are substantially higher than might be expected on a simple proportional basis. The reactions of these two different parts are, however, very similar in regard to segmented cells. Irradiation of the middle part of the body and the combined head and hind part on the other hand, making up some 60 to 65 % of the body is followed by an increase of segmented cells which is at least as high as after whole body irradiation. The behaviour of the lymphocytes is not so well expressed because of the somewhat small effects from the irradiation. It should be noted, however, that only an irradiation of the middle part seems to cause the fall usually found after whole body doses and that in the group head and hind (group 6) the concentration of lymphocytes is high and suggests a possible release of these cells.

In two sets of experiments two groups of animals, each of 10 guinea pigs were irradiated over a left and a right side dorsal field with the other longitudinal half of the body lead shielded (Table 1 series II). The control group and the whole body irradiated group were omitted in this series. The figures for segmented cells and lymphocytes in the first right field irradiation (4669 5971 in Table I) are probably exaggerated since two animals had an extraordinarily high leucocyte level. It may be noted that calculated on a percentage basis the two sets of experiments produced similar results irrespective of the variations in the absolute values.



Table 2

*Significance of the migration of segmented cells and lymphocytes into the circulation when the two abdominal fields were irradiated as compared to each other whole body irradiation or controls*

Cells	Irrad. field	Compared with	Mean change	Animals n	Significance P
Segm.	Right	Left	+ 184.9	48	< 0.001
»	»	Whole body	- 11.3	37	~ 0.2
Lymph.	Left	Right	+ 19.9	48	0.01
»	»	Control	+ 48.3	37	0.005
»	Right	»	+ 3.3	37	0.2-0.3

The data suggest that segmented cells are released in greater amounts following right side irradiation. The difference even in this limited material, is significant on the  $P = 0.01$  level. The lymphocyte concentration is generally high. In view of the fact that the normal concentration is in the order of 3 000 cells and that whole body irradiation causes a further decrease, it appears likely that irradiation of only a longitudinal half of the body produces a release of those cells.

By far the greater part of the liver is involved when the right side of the body is irradiated, whereas only minor parts are affected by left side irradiation. On the other hand, left side irradiation means a substantial irradiation of the intestines and the spleen. The possible role of the spleen was taken into consideration in a group of animals irradiated 6 days after splenectomy had been performed. Splenectomy caused a marked increase in the circulating lymphocytes (about 60 %) but no changes in the segmented cells. An average increase in the segmented cells and a fall in lymphocytes as an outcome of the irradiation is no indication that the spleen has taken part in these reactions. Since in both instances the suprarenals got equal irradiation they may also be assumed to exert no influence.

An appraisal of the experiments now described, although not conclusive, leads to the working hypothesis that a difference exists in the response of the segmented cells to right and left side irradiations. As in the initial trials no significant data were obtained by irradiation of the head and hind parts attention was directed to the middle part of the body.

A definite attempt to ascertain if in a particular case partial body irradiation might initiate specific reactions was made as follows. The irradiated body volume was further limited by using right and left fields of 2.5 cm  $\times$  3 cm. Animals under ether anaesthesia were used. The two fields right and left were placed over the right upper part of the abdomen (liver region) and over

the left inferior part of the abdomen (intestinal region), respectively. The spleen thus received only a small percentage of stray irradiation while each of the suprarenals were in the irradiation fields.

The anaesthetic in itself appeared to produce no changes in the white cells in guinea pigs and the mean values for total leucocytes, and for segmented cells and lymphocytes, did not differ by more than  $\pm 4\%$  from each other in normal and ether treated animals. Nevertheless anaesthesia seems to have a slightly moderating effect on the action of the irradiation, this was at least suggested in the motile segmented group where the outflow of cells was about 25% lower. The difference is significant with a probability of  $P = 0.01$ .

Statistical analyses of the series of right and left field irradiations, as compared to whole body doses and controls were performed in all the combinations that are relevant to the discussion (Table 2). The most marked difference in reaction occurred among the segmented cells in which a right field, as compared to a left field irradiation produced a very high additional outflow. In fact although the irradiated field comprised only about 5% of the body, the release of segmented cells was not significantly different from that following the whole body irradiation. An outflow of lymphocytes was initiated by the left field irradiation and a significant increase of about 50% over the normal level was recorded. There was also evidence that more lymphocytes were forced into the blood circulation following left field irradiation as compared to right field irradiation. The difference in lymphocyte concentration is more or negligible when the right field program is compared with the normal values.

### Discussion

The initial reactions of the white cells following partial irradiation seems to proceed in a different way, as compared to the whole body irradiations. The effect is in a sense specific since irradiation over a right field causes a strong outflow of segmented cells whereas irradiation over a similar area on the left side of the abdomen produces a flow of lymphocytes. The selection of these two fields was made more or less by trial and error. The specificity as regards the migration of segmented cells and lymphocytes is therefore probably not confined to the present irradiation program. The phenomenon as such means a further complication in the analyses of blood reactions shortly after an irradiation. Considered from the practical point of view it should be observed that the results of early analyses of the blood values of irradiated human subjects will depend on what parts of the body have been irradiated. Uniform whole body irradiation is rarely attained and analyses of human cases at an early stage is therefore likely to yield fortuitous results.

The results in the segmented group are uniform in the sense that all the irradiation programs produced an increase in cells in the blood circulation.

Table 2

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The results in the segmented group are uniform in the sense that all the irradiation programs produced an increase in cells in the blood circulation.

It is however noteworthy that so many procedures — whole body, middle part, head and hind part, as well as small right field irradiation, all produce an outflow of segmented cells that is of about the same order of magnitude although the irradiated volume varies up to a ratio of 1:20 (see Table 1). The same holds probably true when the right half of the body is irradiated. The release of segmented cells seems then to be regulated through a mechanism that in the main works independently of the body volume irradiated.

The reaction of lymphocytes is in principal different. An increase in lymphocytes does not appear to occur after whole body irradiation. In our previous material of guinea pigs and mice, lymphocytes started to decrease from the very earliest observations one hour after irradiation, provided the dose reached a certain level. The present material clearly indicates that lymphocytes can be stimulated to an outflow by a left field irradiation over the abdomen, and possibly also by other procedures (cf. Table 1). Because of the omission of controls and a whole body irradiated group, in series II of Table 1, these lymphocyte values cannot be discussed in a conclusive way. The data in Table 2 proves however, with satisfactory significance, the specific reaction of the lymphocytes following a left field dose.

It would appear that the outflow of cells takes place from the irradiated tissue, although the hypothesis of a stimulated release from other parts of the body cannot be eliminated. There is ample evidence that irradiation may cause profound changes in the structure and permeability of tissue membranes especially those that are built up of mucopolysaccharides. BRINAMAN *et al.* (1, 2, 3) have shown that carefully prepared membranes, when irradiated *in vitro* respond rapidly with an increased penetration rate for a limited period of time. The mechanism seems to involve a partial depolymerization of the mucopolysaccharides. Clearly here a neuro-hormonal mechanism is eliminated. Provided similar reactions take place in the intact body — which so far has not been demonstrated — the passage of cells through the barriers of the tissue could be facilitated since the authors noticed that occasionally large particles like red cells could pass through holes in the membranes.

If the hypothesis of a direct outflow from the irradiated tissues be accepted the reaction of the lymphocytes in left field irradiation is not altogether clear. One has to consider that a whole body dose of 300 r causes a decrease in lymphocytes and that then also the left field is included. It may be that also after whole body irradiation an outflow of lymphocytes proceeds from the region of tissues on the left side but that this is masked by the predominating reaction from the major part of the body which may be supposed to favour the opposite reaction, i.e. a disappearance of lymphocytes from the blood circulation. Another explanation may be that whole body irradiation generally prevents release of lymphocytes into the blood, a mechanism that might conceivably be controlled by hormones. We have so far not performed any experiments to verify this hypothesis.

There is however evidence of a hormonal control of at least the leucocyte concentration in the circulation as has also been reported by DOUGHERTY (1952, 1959). When the cortisone in the peripheral blood decreases below a certain level the lymphocytes increase in number, and vice versa. A transient lymphocyte increase, rather similar to that found in the present investigation may also be produced by stress reactions e.g. following the administration of epinephrine. It is, however not known at present whether the resemblance between the radiation induced and the hormonally controlled migrations is more than an incidental one.

### Acknowledgements

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### SUMMARY

The concentration of segmented cells and lymphocytes in the blood four hours after partial body irradiation in guinea pigs was found to differ markedly from that following a whole body dose. The significance of the high release of segmented cells into the blood that occurred when a small field over the right side of the abdomen was irradiated as compared to the release of lymphocytes that was observed after a similar left sided irradiation is discussed.

### ZUSAMMENFASSUNG

Die Anzahl von segmentierten Blutzellen und Lymphocyten schwankt beträchtlich vier Stunden nach Bestrahlung je nachdem ob die Meerschweinchen total oder nur lokal bestrahlt wurden. Die beträchtliche Ausschwemmung von segmentierten Leukocyten in den Blutstrom nach lokaler Bestrahlung des rechten Abdomens steht im Gegensatz zu der hohen Ausschwemmung von Lymphocyten nach Bestrahlung der linken Bauchhälfte.

### RÉSUMÉ

Le nombre des polynucléaires et des lymphocytes dans le sang de cobayes quatre heures après irradiation partielle du corps diffère notablement de celui que l'on trouve après irradiation de tout le corps. Les auteurs étudient la signification de l'importante polynucléose sanguine qui survient après irradiation d'un petit champ du côté droit de l'abdomen et la comparent à la lymphocytose observée après une irradiation analogue du côté gauche.

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## INTERCOMPARISON OF NATIONAL ROENTGEN AND GAMMA RAY EXPOSURE-DOSE STANDARDS

by

H O WYCKOFF A ALLISY G H ASTON G P BARNARD W HUBNER,  
T LOFTUS and G TAUPIN

Many national laboratories maintain free air ionization chambers for the measurement of exposure dose in roentgens. In the past, accurate comparison of these chambers was not possible without the transport of one of the standards to another laboratory where a direct comparison of the instruments was made. Because of the considerable cost and time involved such intercomparisons have not been frequent. On the other hand intercomparisons between national laboratories are necessary to assure worldwide agreement. A more readily portable instrument of sufficient calibration stability for use as a transfer instrument is therefore desirable. This instrument should also be usable in the higher energy regions for example with cobalt 60 and cesium 137 gamma rays.

At the 1956 meeting of the International Commission on Radiological Units and Measurements (ICRU) the U S National Bureau of Standards agreed to construct and calibrate a small cavity chamber a defining diaphragm and a charge compensating capacitor for such indirect intercomparisons. A similar kit has been constructed for the United Nations

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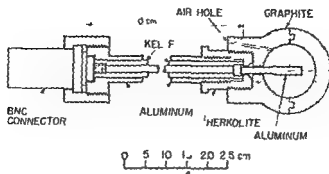


Fig 1 Cross-sectional view of cavity chamber used for intercomparisons

Educational, Scientific, and Cultural Organization These kits are made available to the various national laboratories for intercomparison purposes

The present paper reports the results of the calibration of the ionization chamber instruments by four national laboratories (The results of the diaphragm and capacitor intercomparison are reported elsewhere) These laboratories were chosen for the first calibration because there has been a direct intercomparison between two (U K National Physical Laboratory NPL and U S National Bureau of Standards NBS) of the national standards (ASTON and ARTIX 1956) and indirect intercomparisons between two (French Laboratoire de Dosimetrie LD and U S National Bureau of Standards) of these laboratories (ALFISY ET COLL 1957) and the fourth laboratory (German Physikalisch Technische Bundesanstalt PTB) is in the same geographical region It was hoped that a comparison of the data obtained with the small cavity chambers with that previously reported might indicate the adequacy of the cavity chambers for such intercomparisons The calibration data are reported in some detail By the comparison of data taken at different times by the same laboratory with the same quality of radiation one may obtain some idea about the reproducibility of calibration One may also examine the data to see if there is a trend in the calibration with the geometrical arrangement which is somewhat different in the various laboratories

### Experimental arrangements

A cross sectional view of one of the cavity chambers is shown in Fig 1 It is a three terminal chamber so that the same current measuring system can be used for it as for the standard instrument The wall is about 4 mm thick so that electronic equilibrium will exist even for cobalt 60 gamma rays The diameter of the aluminum center electrode is adjusted empirically so as to reduce the energy dependence as far as possible (Subsequent work

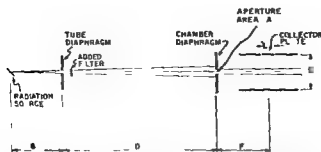


Fig 2 Schematic view of experimental arrangement at each of the national laboratories during the X-ray calibrations. The principal dimensions are labeled. The plate height of the parallel plate free air chamber is dimension G (See Table 1 for numerical values for each of these dimensions. The principal dimensions of the cylindrical standard at PTB are given in fig 3).

with the plastic mixture suggested by SHOCHKA et coll 1958 indicates a similar energy dependence with the plastic.) The ionization collecting potential is applied between the graphite shell and the aluminum tubing. Tests of saturation indicate that the lack of saturation is only about 0.1 per cent for dose rates of the order of a few roentgens per minute when 300 volts are used as the collector potential. All calibrations are therefore made with a 300 volt collecting potential and saturation corrections for this chamber are neglected.

Ionization currents are determined for each polarity of collecting potential. The average of these two currents is reported. In this way extracamerale effects are eliminated and the effect of leakage from strained insulators is reduced.

The schematic arrangement for the measurement of the roentgen beam with a free air chamber at each of the national laboratories is indicated in

Table 1

Principal parameters for free air standard measurements at the laboratories in France, Germany, U.K. and the U.S.

Parameters*	A (cm <sup>2</sup> )	B (cm)	D (cm)	F (cm)	L (cm)	E (cm)	G** (cm)	Field strength v/cm	Field distortion ( $k_f$ )
France	0.7758	14.5	119.5	22.5	6.003	16	20	125	1.000
Germany	0.7879	36	100.2	48.1	25.122	***	***	***	1.004
U.K.	0.8139	25	50	52.4	10.043	30	30	100	1.0006
U.S.	0.7855	20	130	50.8	10.08	20	26.8	240	1.000

\* See Fig 2 for interpretation of the letters

\*\* G is the collector plate height

\*\*\* See Fig 3

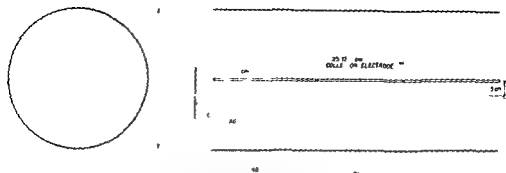


Fig. 3 Schematic view of experimental arrangement at PTB for X-ray calibration. A collecting potential of 3 kV is used and the field strength at radius  $R$  is given by

$$\frac{3000}{r \ln \left( \frac{40}{0.1} \right)} \text{ v cm}^{-1}$$

6

Fig. 2 The important dimensions are indicated by letters. The numerical values for each of the dimensions at each national laboratory are indicated in Table 1. The important dimensions for the cylindrical standard at the PTB are indicated in Fig. 3. Two of the laboratories (PTB and NPL) use a monitoring instrument. This is inserted between the source and the chamber diaphragm. The filtration of this chamber is included when obtaining the indicated half value layer in Tables 4 and 5.

At I D, NBS and PTB the roentgen tubes are operated with a constant potential high voltage generator. At NPL two roentgen tubes cover the 80 to 290 kV range but the generators for each tube at the time of the measurement provided a pulsating potential.

A substitution method is used for the calibration of the cavity chamber at each of the laboratories. The dose rate is first determined by the national standard. The standard is then moved out of the way and the cavity chamber is accurately centered at the position previously occupied by the aperture of the free air chamber diaphragm. After determination of the ionization current in the cavity chamber it is removed and the free air chamber repositioned and the dose rate is determined again.

The dose rate for the 2 MV roentgen beam and for the cobalt 60 and cesium 137 gamma ray beams is determined by means of cavity chambers. The cavity chambers and the corrections used for the 2 MV roentgen beam calibration are described by BARNARD et coll (1956, 1959a, 1959b). The graphite cavity chamber used for the cobalt 60 and cesium 137 gamma ray beam calibrations is described by ARTHUR and RITZ (1957) and the corrections are discussed by WYCKOFF (1960). (The stopping power corrections used for these calibrations are those labeled 'Bakker and Segre' in the paper mentioned here.)

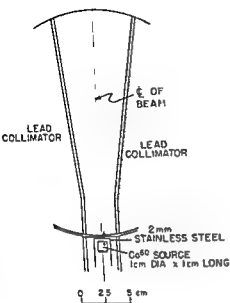


Fig. 4 Cross-sectional view of 100 curie cobalt 60 source and collimator used for gamma ray calibration. The graphite chamber is positioned on the center line of the beam at a distance of approximately 1 meter from the source

The geometrical arrangement of the source and collimation for these calibrations are shown in Figs 4 and 5. Calibration of the gamma ray beams is obtained with the radiation incident at about 45 degrees to the axis of the cylindrical chamber. This is necessary in order to reduce the end wall attenuation discussed by ARTHUR and RITZ.

The 2 MV roentgen beam is produced by electrons accelerated by a Van de Graaff generator. The transmission target is of 2.3 mm thick tungsten and the focal spot is about 0.3 mm diameter. A conical aperture in a tungsten alloy collimator gives a beam of half angle about 43°. The HVL of the radiation is 11.9 mm Cu. Calibrations are performed at 180 cm from the target.

## Results

For the calibrations obtained with free air chambers the calibration factor  $M$  of the cavity chamber is obtained from

$$M = \frac{1.7986 \cdot 10^{11}}{A \cdot L} \cdot \lambda \cdot K_f \cdot \lambda \cdot \lambda_{ph} \cdot \lambda_l \cdot \lambda_p \cdot \lambda_h \cdot \left( \frac{1}{1 - \lambda} + \frac{1}{\lambda_{sc}} \right) \cdot \left( \frac{T}{T_0} \right) \cdot \left( \frac{C}{C_0} \right) \cdot \left( \frac{\Delta v}{\Delta t} \right) \cdot r / \text{amp} \cdot \text{m}^2 \cdot \text{r}$$

- where
- $A$  is the area of the diaphragm in  $\text{cm}^2$
  - $L$  is the length of the collecting electrode in cm
  - $\lambda$  is the correction for air attenuation in a distance  $F$  (see Fig. 2)
  - $\lambda_f$  is the correction for field distortion (see Table I)
  - $f$  is the correction for lack of saturation
  - $\lambda$  is the correction for loss of ionization from secondary electrons because of inadequate plate separation
  - $\lambda$  is the correction for ionization produced by scattered photons
  - $\lambda_h$  is the correction (WEIGHEIM 1938) for shadowing of the collimator by the cable only to the PTB chamber
  - $\lambda_l$  is the correction for radiation leaking into the free air chamber
  - $K_p$  is the correction for radiation penetration of the aperture of the chamber
  - $\lambda_h$  is the correction for humidity
  - $T$  is the absolute temperature in the free air chamber

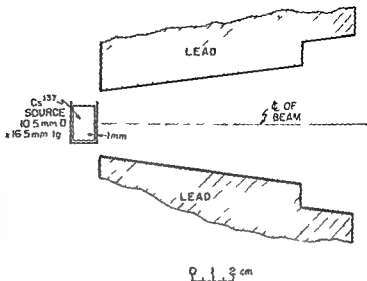


Fig 5 Cross-sectional view of 120 curie cesium 137 source and collimator used for gamma ray calibration. The graphite chamber is positioned on the center line of the beam at a distance of approximately 83 cm from the source.

- $T$  is the absolute temperature in the cavity chamber (assumed to be the same as in the room)
- $C$  is the capacitance in farads of the capacitor used for determining the charge collected from the free air chamber
- $C$  is the capacitance in farads of the capacitor used for determining the charge collected from the cavity chamber
- $\left(\frac{\Delta v}{\Delta t}\right)$  is the rate of change of potential in volt/sec on the capacitor used with the free air chamber and
- $\left(\frac{\Delta v}{\Delta t}\right)$  is the rate of change of potential in volt/sec on the capacitor used with the cavity chamber

Values for  $\Lambda_f$  are obtained by the methods outlined by WYCKOFF and ARTIX (1957). Values of  $\Lambda$  are obtained from the same reference. Values of  $\Lambda$  used at PTB are obtained from the paper by HUBNER (1958). Each of the other three laboratories determined the values experimentally. Values of  $\Lambda_s$  and  $\Lambda$  are obtained either from measurements in the particular laboratory (NPL, NBS) or from the data reported by WYCKOFF and ARTIX. The data for  $\Lambda$  in this reference are corrected in accordance with the more precise values obtained by RITZ (1959) and HENRY (1961). (See correction sheet added to the WYCKOFF and ARTIX reference in 1961.) Values of  $\Lambda_s$  are obtained from the report by BARNARD, ASTON and MARSH (1961). The value of  $K_f$  is obtained experimentally by noting the charge collected when the diaphragm is replaced with a solid plug or by measurements with a thicker diaphragm (NPL). The value of  $\Lambda_p$  is determined by computing the ratio of the radiation transmitted by the border of the aperture to that passed by the aperture.

The data obtained at NBS before cavity chambers II and IX were shipped to the other laboratories are indicated in Table 2. Data obtained after they were returned to NBS are indicated in italics in the same table. The data obtained at LD, PTB and NPL, respectively, are given in Tables 3, 4 and 5. No humidity data are available for some of the calibrations. However, from the recorded temperature and the usual relative humidity encountered during the time of these measurements the estimated correction probably is not more than 0.05 to 0.02 per cent for Table 2 and about twice this for Table 3. When these data were not available these corrections have been neglected in computing the value of  $M$ .

At NBS the exposure time  $\Delta t$  is usually the same for both the free air and the cavity chambers. At LD the value of the capacitor potential was the same for both instruments.

At NPL experience has indicated no difference in the temperature of the interior of the free air chamber and the room. For this laboratory the value of  $T/T_0$  is 1.000.

An additional correction  $k$ , is applied at NBS because of the lack of coplanarity of the guard plates and the collector plate. Earlier measurements (Ritz 1960) indicated that  $k = 1.0015$ . Measurements made after the calibrations reported here indicated that the correction is still the same.

For the gamma ray and 2 MV roentgen calibrations the calibration factor is given by

$$M = \frac{R}{C} \left( \frac{\Delta v}{\Delta t} \right) \left( \frac{T}{273.2} \right) \left( \frac{760}{P} \right) k \quad (2)$$

where

$R$  is the exposure dose rate at the calibration point in r/min,

$P$  is the atmospheric pressure in mm of mercury and the other symbols having the meaning previously described.

Results of such calibrations are given in Table 6.

One of the investigators (G. P. BARNARD) noted a  $\pm 0.2$  per cent variation of response with direction of incident 2 MV radiation on chamber II but none on chamber IX. No investigation for such a possible orientation dependence was conducted before the chambers left NBS but an attempt was made to verify the NPL results after the chambers were returned. In agreement with NPL no orientation dependence greater than the reproducibility (about 0.1 per cent) was observed for chamber IX with cobalt 60 gamma rays. The results for chamber II are less certain. Shortly after the chambers were returned to NBS chamber II developed an intermittent electrical short between the center electrode and the grounded aluminum tube. Radiograms indicated that the collecting electrode was not positioned on a diameter of the cavity. Forced rotation of the center pin of the BNC connector which connects directly to the collecting electrode, moves the center electrode on the surface

Table 2

Data from National Bureau of Standards at the start and end of intercomparison  
(The values from the end of the intercomparison are in italics)

kV	Total filtration mm		HVL (mm Cu)	Approx dose rate (r/min)	Free air chamber corrections *			
	Al	Cu			$A_1$	$A_2$	$A_3$	$A_4$
60	4.4	0	0.089	0.67	1.013 <sub>1</sub>	1.000 <sub>1</sub>	1.000	1.000
75	4.4	0	0.11	1.12	1.011 <sub>1</sub>	1.000 <sub>1</sub>	1.000	1.000
100	5.4	0	0.20	1.69	1.009 <sub>1</sub>	1.000	1.000	1.000
150	5.4	0.25	0.66	2.3	1.006 <sub>1</sub>	1.001 <sub>1</sub>	1.000	1.000

Table 2 (cont.)

K		Chamber	Date	$\left(\frac{\Delta v}{\Delta t}\right)$	$\frac{T}{T}$	R <sub>a</sub>	M 10 <sup>4</sup> (r/amp min)			
K	K <sub>ex</sub>			$\left(\frac{\Delta v}{\Delta t}\right)$						
0.000	0.007	II	2/6/59	0.7576	1.000		1.806			
			2/13/59	0.7509	1.000		1.801			
			5/9/60	0.7900	1.000	1.000	1.802			
			1/10/61	7.75	1.000	1.000	1.801			
		IX	1/18/59	0.7179	1.001		1.724			
			2/14/59	0.7174	1.001		1.722			
			5/5/60	0.7541	1.000	1.000	1.721			
			5/9/60	0.7542	1.001	1.000	1.722			
		1/10/61	7.453	1.000	1.000	1.731				
			0.000	0.007	II	2/6/59	0.7427	1.000		1.779
						2/13/59	0.7413	1.000		1.775
						5/10/60	0.7784	1.000	1.000	1.772
1/10/61	0.7330	1.001				1.000	1.772			
IX	1/18/59	0.7089			1.002		1.700			
	2/13/59	0.7061			1.001		1.693			
	2/14/59	0.7076			1.001		1.696			
	5/5/60	0.7442			1.000	1.000	1.695			
1/10/61	0.7032	1.001			1.000	1.700				
	0.000	0.006			II	2/6/59	0.7264	1.001		1.740
						2/13/59	0.7258	1.000		1.738
						5/10/60	0.7613	1.001	1.000	1.734
1/10/61			0.7182	1.002		1.000	1.738			
IX			1/18/59	0.6932	1.002		1.662			
			2/13/59	0.6907	1.001		1.654			
			2/14/59	0.6926	1.001		1.659			
			5/5/60	0.7163	1.001	1.000	1.654			
1/10/61			0.6846	1.002	1.000	1.67				
			0.001	0.004	II	2/6/59	0.7161	1.001		1.717
						2/14/59	0.7151	1.002		1.716
						5/10/60	0.7523	1.001	1.000	1.715
1/10/61	0.7119	0.992				1.000	1.719			
IX	1/18/59	0.6787			1.002		1.629			
	2/14/59	0.6784			1.001		1.626			
	5/6/60	0.7112			1.000	1.000	1.619			
	1/10/61	0.6710			0.999	1.000	1.619			



Table 2 (cont.)

kV	Total filtration mm		HVL (mm Cu)	Approx dose rate (r/min)	Free air chamber corrections *			
	Al	Cu			$A_e$	$A_s$	$A_I$	$A_p$
200	5.4	0.52	1.76	3.6	1.005	1.001 <sub>4</sub>	1.000	1.000
230	5.4	1.02	2.17	4.7	1.003 <sub>2</sub>	1.001	1.000	1.000
250	5.4	3.15	3.2	2.4	1.004 <sub>2</sub>	1.001	1.000	1.000

\* In eq 1 the value of  $\frac{1.7986 \cdot 10^{13}}{\lambda L} K_f A_e = 0.22750 \cdot 10^4$  for the 1959 data  $\frac{C}{C} = 10.469$  for the 1960 data  $\frac{C}{C} = 9.9475$  for the 1961 data at 60 kV  $\frac{C}{C} = 1.0142$  and for the remainder of the 1961 data  $\frac{C}{C} = 10.558$

of an imaginary small cone. Apparently, the axis of the collecting electrode and its connection are not the same.

Measurements on the radiograms of this chamber also indicated no large differences in wall thickness such as might exist if the outer and inner sphere did not have the same center. The uncertainty (0.1 to 0.2 mm) in such measurement, however, is large enough so that this reason for orientation de-

Table 2 (cont.)

K	A	Chamber	Date	$\left(\frac{\Delta v}{\Delta t}\right)_s$	$\frac{T}{T'}$	$K_A$	M $10^{-11}$ (r/amp min)
				$\left(\frac{\Delta v}{\Delta t}\right)$			
0 004	0 004	II	2/6/59	0 7200	1 001		1 731
			2/14/59	0 7193	1 002		1 730
			5/10/60	0 7583	1 001	1 000	1 737
			1/10/61	0 7138	1 000	1 000	1 728
		IX	1/18/59	0 6796	1 003		1 636
			2/14/59	0 6788	1 001		1 632
			5/6/60	0 7118	1 000	1 000	1 574
			1/10/61	0 6716	1 000	1 000	1 626
		II	2/6/59	0 7254	1 001		1 744
			2/14/59	0 7254	1 002		1 746
			5/10/60	0 7620	1 001	1 000	1 747
			1/10/61	0 7214	1 007	1 000	1 752
		IX	1/18/59	0 6818	1 001		1 644
			2/14/59	0 6825	1 001		1 642
			5/6/60	0 7155	1 001	1 000	1 635
			1/10/61	0 6761	1 001	1 000	1 640
0 005	0 003	II	2/6/59	0 7303	1 001		1 754
			2/14/59	0 7321	1 002		1 759
			5/10/60	0 7713	1 001	1 000	1 760
			1/10/61	0 7278	1 007	1 000	1 765
		IX	1/18/59	0 6857	1 004		1 650
			2/14/59	0 6860	1 002		1 649
			5/6/60	0 7189	1 000	1 000	1 640
			1/10/61	0 6788	1 003	1 000	1 647

Estimated

pendence of calibration cannot be ruled out. Calibrations of chamber II at NBS indicated that the orientation dependence may be as large as reported by NPI but the reproducibility is of the same order (about 0.1 per cent). Such calibrations included determinations with cobalt 60 gamma rays and with 100 kV roentgen rays. The latter determinations also included different orientations of the collecting electrode.

**Table 3**  
*Data from Laboratoire de Dosimétrie*

kV	Added filter (mm)		HVL (mm Cu)	Approx. dose rate (r/min)	Free air chamber corrections			
	Al	Cu			$K_a$	$F$	$F_1$	$K_p$
60	1.2	—	0.08	0.36	1.009	1.001	1.000	1.000
100	1.8	—	0.2	0.38	1.007	1.001	1.000	1.000
150	1	0.25	0.65	1.35	1.005	1.001	1.000	1.000
200	1	0.5	1.2	2.12	1.004	1.001	1.000	1.000

\* The HVL in copper at 60 kV was not measured at the Laboratoire de Dosimétrie but the HVL in aluminum was determined to be 2.85 mm. As this agrees very well with the HVL in aluminum (2.9 mm) determined at NBS it is assumed that the HVL in copper for 60 kV X rays is the same as that obtained at NBS.

The reason for the orientation dependence has not been definitely established at this time but care should be taken to minimize the probability of its happening in the future. Radiograms of the chamber after construction will check the centering of the collector electrode. The chamber could be calibrated always in the same orientation. This is now the standard practice at NBS. While the magnitude of the orientation dependence is probably not large it is suggested that these two precautions be observed for future intercomparisons.

### Comparison of results

An examination of the results listed in Table 2 permits an evaluation of the reproducibility of the cavity chamber calibration. In order to eliminate possible changes of these calibrations between the two sets, it is necessary to examine separately the data taken before and after shipment. The maximum deviation of any calibration from the mean value obtained for either chamber at any one quality varies from about 0.03 to 0.3 per cent. The mean value of these

Table 3 (cont.)

$K$	$K_{sc}$	Chamber	$\frac{\Delta v}{\Delta v}$	Date	$\frac{T}{T}$	$M \cdot 10^4$ (r/amp min)
0 000	0 006	II	1 000	4/21/59	0 9953	1 794
0 000	0 004	II	1 000	4/15/59	0 9983	1 741
				4/14/59	0 9971	1 737
				4/15/59	0 9958	1 735
				4/17/59	0 9980	1 737
				4/21/59	0 9932	1 741
0 003	0 003	II	1 000	4/10/59	0 9976	1 715
				4/14/59	0 9960	1 714
				4/16/59	0 9986	1 712
				4/20/59	0 9986	1 718
0 007 <sub>1</sub>	0 003	II	1 000	4/14/59	0 9970	1 728
				4/15/59	0 9974	1 727
				4/17/59	0 9969	1 725
				4/21/59	0 9988	1 730

\* In eq 1 the value of  $\frac{1.7986 \cdot 10}{4 L} K_f = 0.38621 \cdot 10$   $\frac{C}{C} = 9.76\%$

deviations for all qualities for either chamber is about 0.1 per cent. Similar ranges and mean values are obtained from the data in the other tables where there are sufficient data for analysis.

A comparison of the two sets of data from NBS permits a determination of the long term stability of the calibration. The ratio of the mean calibration factor in the first set to that in the second set for the same quality is taken as a measure of the long term stability. For chamber II this ratio varies from about 0.997 to 1.003 for the different qualities and the mean value for all qualities is 1.000. For chamber IX the ratio varies from about 0.999 to 1.006 with a mean value of 1.003.

Thus there appears to be a reproducibility uncertainty of as much as 0.3 per cent for either chamber when only a small number of measurements are available. In addition there appears to be a possible orientation dependence of up to 0.2 per cent for chamber II and a drift of calibration of up to 0.3 per cent for chamber IX. These factors set the maximum uncertainty of the calibration at about 0.5 per cent. Thus one might expect that the lack of reproducibility

Table 4

*Data from the Physikalisch Technische Bundesanstalt*

kV	Added filter (mm)		HVL (mm Cu)	Approx. dose rate (r/min)	Free air chamber corrections			
	Al	Cu			F	K	K <sub>ab</sub>	K <sub>t</sub>
60	—	—	0.083	0.28	1.021	1.000 <sub>4</sub>	1.001	1.000
75	—	—	0.110	0.58	1.018 <sub>4</sub>	1.000	1.001 <sub>1</sub>	1.000
100	1.0	—	0.197	1.02	1.014 <sub>4</sub>	1.000	1.001 <sub>1</sub>	1.000
150	1.0	0.13	0.64 <sub>7</sub>	1.15	1.011	1.000	1.001	1.000
200	1.0	0.26	1.20	1.00	1.010	1.000	1.001 <sub>1</sub>	1.000
200	1.0	0.26	1.20 <sub>4</sub>	1.00	1.010	1.000 <sub>4</sub>	1.001	1.000
250	1.0	0.72	2.11	1.18	1.009	1.000	1.001 <sub>1</sub>	1.000
250	1.0	3.0	3.13	1.12	1.008	1.000	1.001	1.000
250	1.0	3.0	3.13	1.12	1.008	1.000	1.001 <sub>1</sub>	1.000
300	1.0	4.0	3.95	1.10	1.008	1.000	1.001 <sub>1</sub>	1.000
350	1.0	6.0	4.74	1.10	1.008	1.000	1.001	0.9918

\* Inherent filtration about 4 mm Al

\*\* In eq. 1 the value of  $\frac{1.7986 \cdot 10}{A \cdot L} F_f = 0.091231 \cdot 10$ 

of the calibration of either chamber at any laboratory for any quality should not exceed about 0.5 per cent.

As the data from the four laboratories are not all obtained for the same qualities it is necessary to interpolate in order to compare the results. The calibration factor obtained for the two chambers at the four laboratories are plotted against the half value layer (HVL) of the radiation in Figs. 6 and 7. The vertical line for each NBS calibration indicates the range of values obtained while the circle indicates the mean value. For clarity only the mean values are plotted for the other laboratories. A smooth curve is drawn through the

Table 4 (cont.)

$K_p$	$\frac{1}{1-K'K''}$	Chamber	Date	$\left(\frac{C}{C}\right) \frac{\left(\frac{\Delta v}{\Delta t}\right)}{\left(\frac{\Delta v}{\Delta t}\right)}$	$\frac{T}{T_c}$	$A_A$	M $10^{-11}$ (r/amp min)
1 000	0.9896	II	6/8/59	19 499	1 001	1 0017	1 808
		IX	6/8/59	18 685	1 001		1 732
1 000	0.9899	II	6/1/59	19 248	0.999	1 0013	1 773
		IX	6/1/59	18 418	0.998		1 696
1 000	0.9913	II	5/28/59	18 930	1 000	1 0011	1 743
		IX	5/28/59	18 016	1 001		1 660
1 000	0.9933	II	6/3/59	18 629	1 000	1 0012***	1 713
		IX	6/3/59	17 726	1 001		1 630
1 000	0.9943	II	6/2/59	18 716	1 000 <sub>2</sub>	1 0011	1 723
		IX	6/2/59	17 654	1 000 <sub>1</sub>		1 625
1 000	0.9943	II	6/11/59	18 756	1 000 <sup>2</sup>	1 0011	1 727
		IX	6/11/59	17 698	1 001		1 628
1 000	0.9934	II	5/29/59	18 918	1 001	1 0008 *	1 740
		IX	5/29/59	17 735	1 001		1 632
1 000	0.9940	II	6/4/59	19 051	1 000	1 0005	1 748
		IX	6/4/59	17 826	1 001		1 637
1 000	0.9940	II	10/13/59	19 077	1 000 <sup>2</sup>	1 0004	1 748
		IX	10/13/59	17 888	0.999		1 638
1 000	0.9963	II	10/13/59	19 079	0.999	1 0003	1 752
		IX	10/13/59	17 931	1 000		1 647
0.9983	0.9973	II	10/14/59	19 368	0.999	1 0003	1 763
		IX	10/14/59	18 113	1 001		1 650

\*\* Estimated

NBS roentgen data points. The large value for the softer qualities results from the large wall attenuation which decreases for the harder radiations. The rise beyond the minimum is due to the decrease of the photoelectric effect in the aluminum center electrode.

The deviation of the calibration factors obtained at LD, NPL and PTB from the smooth curve through the NBS results are listed in Table 7. Column 3 of that table gives the deviations for chamber II, column 4 for chamber IX, and column 5 the mean value for the two chambers at each of the qualities. The maximum difference between columns 3 and 4 is 0.9 per cent for one

**Table 5**  
*Data from National Physical Laboratory*

kV	Added filter * (mm)		HVL (mm Cu)	Approx dose rate (r/min)	Free air chamber corrections			
	Al	Cu			<i>F</i>	<i>K</i>	<i>K<sub>p</sub></i>	<i>A<sub>t</sub></i>
80	—	—	0.103	2.1	1.023	1.00 <sup>2</sup>	1.000	1.000 <sub>1</sub>
125	1.0	—	0.200	4.3	1.015	1.004 <sub>1</sub>	1.000	1.000
125	1.0	0.05	0.250	3.4	1.014	1.003	1.000	1.000
145	1.0	0.25	0.50	2.7	1.011 <sub>1</sub>	1.002	1.000	1.000
180	—	—	1.02	3.4	1.010 <sub>1</sub>	1.003	1.000	1.000
250	1.0	0.1	1.53	5.7	1.009	1.005	1.000	0.999
290	1.0	0.63	2.19	6.4	1.008	1.006 <sub>1</sub>	1.000	0.998
250	1.0	1.9	2.55	2.6	1.008 <sub>2</sub>	1.002	1.000	0.998
290	1.0	4.0	3.40	2.5	1.007	1.002	1.000	0.995

\* From 80 to 145 kV the tube had an inherent filtration equivalent to about 0.095 mm Cu and at higher voltages to about 1.1 mm Cu. The monitor provided a permanent additional filtration of 8 mm perspex.

quality but the next highest difference is 0.6 per cent and the remainder are 0.4 per cent or less. These differences are consistent with the expected reproducibility noted above.

Table 5 (cont.)

A	A	Cavity chamber number	Date of measurements	P <sup>00</sup>	A <sub>A</sub>	M 10 <sup>1</sup> (r/amp min)
0 000	0 00b	11	12/8/59	1 760 <sup>7</sup>	1 001	1 796
		11	12/14/59	1 7693	1 001 <sub>1</sub>	1 805
		1X	1/16/60	1 6774	1 001	1 711
		1X	1/8/60	1 6811	1 000	1 715
0 000	0 006	1X	1/7/60	1 6334	1 000	1 663
		1X	1/8/60	1 6445	1 000	1 669
0 000	0 006	11	12/9/59	1 7066	1 000	1 728
		11	12/15/59	1 7030	1 001	1 727
0 000	0 006 <sub>1</sub>	11	12/9/59	1 6846	1 000	1 701
		11	12/14/59	1 6989	1 000	1 715
		11	12/15/59	1 6962	1 000	1 713
		1X	1/7/60	1 6104	1 000	1 626
		1X	1/11/60	1 6138	1 000	1 629
0 000	0 005	11	12/9/59	1 7007	1 000	1 718
		11	12/11/59	1 7036	1 000	1 721
		1X	12/31/59	1 6124	1 000	1 628
		1X	1/11/60	1 6109	1 000	1 627
0 001	0 005	11	1/27/60	1 7291	1 000	1 750
		11	1/28/60	1 7293	1 000	1 750
0 00 <sup>7</sup>	0 004	11	12/22/59	1 7466	1 000	1 768
		11	1/25/60	1 7376	1 000	1 758
		1X	1/4/60	1 6341	1 000	1 654
		1X	1/18/60	1 6338	1 000	1 653
0 002	0 004	11	12/10/59	1 7431	1 000	1 757
		11	12/16/59	1 7421	1 000	1 756
0 001	0 004	11	12/10/59	1 7498	1 000	1 758
		11	12/11/59	1 7565	1 000	1 764
		1X	1/20/60	1 6553	1 000	1 663
		1X	1/21/60	1 6531	1 000	1 660

$$P = \frac{1.7986 \cdot 10}{A \cdot L} \left( \frac{C}{C} \right) \left( \frac{\frac{J}{Jt}}{\frac{Jv}{Jt}} \right)$$

It is noted that the average calibration factors obtained at NPL tend to be larger than those obtained at NBS and those at PTB seem to be lower especially at the harder qualities. Those at LD are in close agreement but



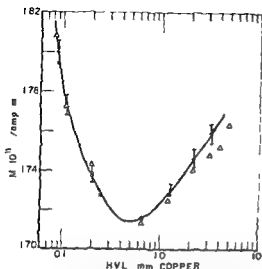


Fig. 6 Average calibration factors for chamber II obtained at the four laboratories for the various qualities  $\square$  = LD  $\nabla$  = NBS  $\bullet$  = NPL  $\triangle$  = PTB. The vertical line through each NBS point gives the range of values obtained.

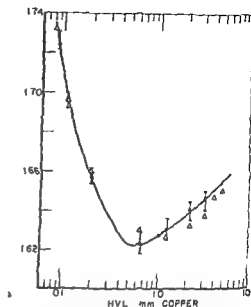


Fig. 7 Average calibration factors for chamber IX obtained at three laboratories for the various qualities  $\nabla$  = NBS  $\bullet$  = NPL  $\triangle$  = PTB. The vertical line through each NBS point gives the range of values obtained.

cover only a limited range of qualities. There has been no previous intercomparison between NBS and PTB but the previous indirect intercomparison between LD and NBS and the previous direct intercomparisons between NPL and NBS gave results similar to the present ones. The last column of Table 7 indicates the deviations previously obtained (ALLISY et coll 1957, and ASTON and ARTHUR 1956) for approximately the indicated qualities. It is seen that these values differ from those obtained in the present intercomparisons by not more than the expected amount (0.5 per cent). While the previous NBS-NPL intercomparisons were obtained with a d.c. generator for the roentgen tube, the present results are obtained with a pulsating potential at NPL and a d.c. generator at NBS. The good agreement between columns 5 and 6 indicates that the effect of this different wave form is not greater than the possible lack of reproducibility, 0.5 per cent.

For the previous NBS-NPL intercomparison the dose rates and target-diaphragm distances were the same for both chambers and determinations were made at the same collecting field strengths. During the present measurements, the dose rates, target-diaphragm distances and field strengths were all different at the two laboratories. The saturation corrections  $K'$  were

Table 6

Source	High energy calibrations			
	HVL (mm Cu)	Chamber	Date	$M \cdot 10^{-11}$ (r/amp min)
$\text{Co}^{60}$ (NBS)	14.7	II	2/9/59	1.780
		IA	2/9/59	1.663
$\text{Cs}^{137}$ (NBS)	10.5	II	2/10/59	1.788
		IA	2/11/59	1.680
2 MV roentgen rays (NPL)	11.9	II	2/16/60	1.774
			2/19/60	1.771
			3/4/60	1.770
		IA	2/16/60	1.650
			3/3/60	1.648
			3/4/60	1.649
$\text{Co}^{60}$ (NBS)	14.7	II	5/19/60	1.793
			5/19/60	1.774
			5/20/60	1.773
		IA	1/6/61	1.775
			5/19/60	1.650
			5/30/60	1.655
$\text{Cs}^{137}$ (NBS)	10.5	II	1/6/61	1.659
			5/19/60	1.794
		IA	5/29/60	1.799
			5/16/60	1.666
			5/20/60	1.667
			5/29/60	1.673

determined at each laboratory under the conditions used at that laboratory. Further investigations are needed to assure that these are consistent.

As noted earlier the NPL results tend to be higher than NBS and PTB lower for the harder qualities. Moreover the present results for NPL are in moderately good agreement with those obtained earlier. Good agreement in the area of diaphragms and in the value of the capacitance used for current measurement (ICRU Report 1959) seem to rule out these factors as contributing to these differences. In any case because both the NPL and PTB chambers are larger than the NBS chamber the differences cannot be attributed to a simple function of chamber size. Perhaps detailed redetermination of the correction factors will be necessary in order to obtain a reason for these differences.

The measurements with gamma rays and 2 MV roentgen rays give less useful intercomparison. The large spread in the NBS calibration factors and the large difference in the spectra of the roentgen and gamma ray sources make a comparison difficult. In view of these difficulties the intercomparisons seem reasonable.

Table 7

*Comparison of calibration factors—deviation of calibration factor from ABS (per cent)*

HVL (mm Cu)	Lab	Chamber II	Chamber IV	A <sub>1</sub>	Previous**
0.083	PTB	-0.1	-0.1	-0.1	
0.089	LD	-0.4	—	-0.4	0.0
0.103	NPL	+0.8	+0.4	+0.6	+0.5
0.11	PTB	0.0	0.0	0.0	
0.197	PTB	+0.3	+0.2	+0.3	
0.20	LD	+0.1	—	+0.1	+0.1
0.20	NPL	—	+0.6	+0.6	+0.4
0.25	NPL	0.0	—	0.0	+0.4
0.50	NPL	-0.2	+0.2	0.0	+0.3
0.64 <sub>7</sub>	PTB	-0.2	+0.4	+0.1	
0.65	LD	0.0	—	0.0	+0.4
1.02	NPL	-0.3	+0.0	-0.2	+0.3
1.2	LD	-0.1	—	-0.1	-0.1
1.20	PTB	-0.2	-0.2	-0.2	
1.53	NPL	+0.8	—	+0.8	+0.4
2.11	PTB	-0.3	-0.4	-0.4	
2.19	NPL	+1.0	+0.8	+0.9	+0.5
2.50	NPL	+0.2	—	+0.2	
3.13	PTB	-0.6	-0.5	-0.6	
3.4	NPL	0.0	+0.9	+0.5	
3.95*	PTB	-0.8	-0.2	-0.5	
4.74*	PTB	-0.6	-0.3	-0.5	

\* Deviations uncertain at this quality as an extrapolation of NBS data is involved

\*\* For approximately the indicated HVL

### Conclusions

Indirect intercomparisons of calibrations of ionization chambers for exposure dose measurements in roentgens have been completed between the national standards of France, Germany, U.K., and U.S.A. with an estimated maximum uncertainty of about 0.5 per cent. This is somewhat larger than that assigned to direct comparisons (ASTON and ARTHUR 1957). This large uncertainty can probably be reduced by a factor of about 2 by (1) assuming that there is no drift in calibration before the intercomparison is attempted, (2) radiographing the chambers before use to see that they are as symmetrical as possible, and (3) always calibrating the instrument in a fixed orientation. Under these conditions such indirect intercomparisons should be almost as accurate as the direct ones.

The present calibrations agree with those obtained earlier between three of the laboratories to within the expected uncertainty, 0.5 per cent, also the

calibrations at PTB agree with those at NBS to within 0.6 per cent. However the results from NPL and PTB disagree by slightly more than one per cent for nearly the same quality of the harder radiations. A detailed redetermination of some of the correction factors may be needed to remove this discrepancy.

### Acknowledgement

The measurements at NPL were mostly made by Mr A. R. S. Marsh and Mr J. E. Woodall. Many of the measurements at NBS were made by Mr L. DeLaVergne and Mr J. T. Weaver. The work described above has been carried out as part of the research programs of the several laboratories and this paper is published by permission of their directors.

### SUMMARY

A pair of cavity ionization chambers has been circulated to the national laboratories of France, Germany, U. K. and U. S. A. for calibration with roentgen and gamma rays. The difference of their calibrations with a given quality of radiation is taken as a measure of the disagreement of the national standards. The results obtained agree with some earlier direct comparisons to within the expected uncertainty of these measurements — about 0.5 per cent.

### ZUSAMMENFASSUNG

Ein Paar Hohlraumionisationskammern haben zum Zweck der Kalibrierung in den staatlichen Laboratorien von Frankreich, Deutschland, U. K. und U. S. A. zirkuliert. Die Differenz der Kalibrierungsfaktoren bei einer gegebenen Strahlenqualität wird als Mass für die Abweichungen zwischen den nationalen Standardmethoden angenommen. Die erhaltenen Resultate stimmen mit einigen früheren direkten Vergleichen innerhalb einer Fehlergrenze von ca. 0.5 % überein.

### RÉSUMÉ

Les auteurs ont envoyé aux laboratoires nationaux d'Allemagne, de France, du Royaume Uni et des U. S. A. deux chambres d'ionisation à cavité pour étalonnage avec les rayons roentgen et gamma. La différence d'étalonnage avec une qualité donnée de rayonnement est considérée comme une mesure de la discordance des étalons nationaux. Les résultats obtenus concordent avec certaines comparaisons directes préalables dans l'intervalle d'incertitude prévisible de ces mesures, environ 0.5 pour cent.

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## BOOK REVIEWS

**KÜNSTLICHE RADIOAKTIVE ISOTOPE IN PHYSIOLOGIE, DIAGNOSTIK UND THERAPIE 2. Auflage**  
Band I und II Herausgegeben von H. Schwiege und F. Turba 2 575 Seiten und 759 Ab-  
bildungen Springer Verlag Berlin 1961 Price DM 398

The rapid increase in the use of radioisotopes for the most varied purposes in the medical sciences is well reflected in the fact that the second edition of the well known handbook of Schwiege has grown to more than double the size of the first edition. It contains contributions from 83 authors, mostly German and American, writing in their respective languages, one chapter is in French. About 330 of the 2 575 pages contain lists of references, while the subject index fills 270 pages. It is clearly impossible within a reasonable space to review in detail a work such as this, and there is probably no single person in the world able critically to judge all parts of so varied a subject matter. The present reviewer can claim competence only within small realms of the subjects treated.

The first volume begins with a long chapter on general methods for detecting radioisotopes, although without any detailed treatment of the electronic instruments in use, and a still longer one on the different radioisotopes and the preparation of various compounds and samples for measurement. There are chapters on autoradiography, radiobiology, radiation protection, and the construction and equipment of nuclear medicine laboratories.

A few chapters on general aspects on the use of radioisotopes in biochemistry, physiology, etc. are followed by a number of chapters with detailed treatment of various special problems.

The second volume begins with chapters on several of the most important elements and their radioisotopes. Very little information is, however, given on half-lives and radiation properties. The chapter on iron describes in detail the normal and pathologic metabolism of the element and hematologic applications of radio-iron.

Other chapters concern muscle and nerve physiology, various metabolic studies and applications of radioisotopes in bacteriology, virology, and immunology. Some of the chapters that follow have more direct diagnostic interest (circulation research, tumour diagnosis, thyroid function studies, the biochemistry of vitamin B12).

The last chapters are concerned with therapeutic uses (tumour therapy, hematology, thyroid therapy). Uses of radioisotopes in sealed containers for internal or external irradiation, including telegamma therapy, are also described, though relatively briefly. A chapter on the therapeutic use of high energy heavy ions falls outside the scope of the book as defined in its title as, in the diagnostic part, do the references to uses of stable isotopes.

As far as the reviewer can judge, the editors and the authors have done a good job, and no cause for any major criticism has been found. Several duplications are of course unavoidable when different authors treat closely related subjects, but they seem to be innocuous and some times even useful.

The work may be considered indispensable to general medical libraries and to radiological and biophysical institutes. Many research workers will also find it worth its relatively high price, even though they may have practical use of only a fraction of its contents.

Sten Benner

~~THE INITIAL EFFECTS OF IONIZING RADIATIONS ON CELLS~~ A Symposium held in Moscow October 1960 Edited by R J C Harris 367 pages 129 illustrations and 24 tables Academic Press London 1962 Price 75 sh

These are the proceedings of a Symposium in Moscow in the autumn of 1960 supported by UNESCO IAEA and the Academy of Sciences USSR

The word initial is not to be taken literally since irradiation effects that become apparent days or even weeks after the irradiation were also discussed All the usual subjects of radiation biology were covered at the meeting

The particular interest in this symposium lies in the fact that a substantial presentation of Soviet radiobiology becomes available in English nearly fifty per cent of the contributions being from Soviet scientists There were many interesting communications The material in some of the Russian papers was evidently condensed from years of work and references about interesting details are sometimes made to original publications in the Russian language

Of the papers that seem to present new lines of research and new technical ideas may be mentioned FRANK's studies on rhythmic changes in oxidative processes A micropolarographic device was developed to study these phenomena MEISSEL et alii have applied fluorescence microscopy to the study of irradiation effects on nucleic acids and proteins

The symposium was concluded by a general discussion on topics of particular interest selected from the material presented in the individual papers

*A Forsberg*

FUNDAMENTALS OF RADIOBIOLOGY By Z M Bacq and Peter Alexander Second completely revised edition 555 pages 150 illustrations and 81 tables Pergamon Press Oxford 1962 Price 70 sh

This well known book now appears in the International Series of Monographs on Pure and Applied Biology in what is virtually an entirely revised form of the first edition The great amount of experimental work that has been done in the last decade is at once apparent from a perusal of the text Radiation biology in its present stage encompasses large tracts of the sciences of chemistry and biology and also needs a fair knowledge of the fundamentals of physics A survey of radiation biology is certainly a taxing enterprise for two authors although a combination of a physics chemist and a physiologist probably comes closest to the ideal combination The selection of the material must nevertheless to some extent reflect their interests and scientific fields particularly as it is virtually impossible to cover the whole material in some 500 pages To quote the preface This is a survey and not a monograph We have selected certain investigations from the enormous mass of published material

Subjects such as the radiation chemistry of macromolecules and some parts of mammalian radiobiology as the biochemistry physiology and pathology of the irradiated body are comprehensively treated and the same applies to protection The rapid development in the important field of radiation genetics is outlined in a few pages but with references as in other instances to modern reviews The book is written in a vivid and entertaining way which reflects the enthusiasms of the authors and makes for easy reading The personal views of the authors in many controversial questions as the merits of the physical target theory in radiation biology are clearly expressed

*A Forsberg*

## VI SYMPOSIUM NEURORADIOLOGICUM ROMA

18-22 September 1961

### THERAPY & BIOLOGY SECTIONS

The titles of some of the papers read at the symposium but not submitted for publication in *Acta Radiologica* are included in the table of contents given below

BREIT A. Passau	Neue Erkenntnisse bei der experimentellen Bestrahlung des Nervensystems (not received)	—
CRANDALL P H and WEST OVER J L Los Angeles	Technique and dosimetry of yttrium 90 thalamotomy	82
GALPERIN M D and PIL B V Leningrad	Treatment with irradiation of patient with cerebral tumors (not received)	—
GASLOFF H Munchen	EEG-changes in X irradiated rabbits (not received)	—
HÄKANSSON C H and LIND- GREN M Lund	EEG-changes following irradiation of brain tumors (Proc Symp Vienna 1961 publ by Intern Atomic Energy Agency # 77 Vienna 1962)	—
MARAS H New York	Hemangioblastoma cerebelli — report of a six year survival after roentgen therapy by tumor oscillation trough a grid	95
RICH E New York	Ionizing radiations and the mammalian embryo	101
SWEET W H SOLOWAY A H and BROWNELL G L Bos- ton	Boron slow neutron capture therapy of gliomas	114
TOPOL O Prag	Zur Aktinotherapie der Hirngeschwulste (not received)	—
WENDE S Berlin	Nachweis von cerebralen Strahlenschaden mit radioaktiven Substanzen	122



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*A Forsberg*

amounts sufficient to destroy small interior areas of the brain. It may be that different methods will be applicable to different parts of the nervous system. We have applied our efforts to the goal of destruction of the ventrolateral nucleus of the human thalamus for the treatment of dyskinesia.

Some understanding of the unpredictable results of the various methods can be achieved by considering the physical nature of the area, as has been stated by ARONOW. Thalamic nuclear masses are relatively well vascularized. The vascular fluid channels make the convection of heat variable and complex, electrical properties irregular, and mechanical punctures particularly if repeated, fraught with danger of hemorrhage. Also, the brain tissue is a poor conductor of heat and the fluids of the region when heated to steam and gas make irregularities in the size and shape, especially in larger lesions. Gray matter also has a higher resistance to temperature than the white matter of the nearby internal capsule. Because of the lower threshold of the capsule, it may be affected before the nuclear masses are completely destroyed. Another variable circumstance of this particular region and the distribution of some forms of energy is the nearby presence of either air-filled or fluid-filled ventricles. In either case, these ventricles affect the distribution of heat loss of heat or electrical change. The rate of change brought about by these methods (i.e., rapidity of destruction) must be considered in relation to the shock to the nervous system and the effects of increasing the surrounding edema or other partial damage in nearby regions.

Ionizing radiation was investigated to achieve circumscribed lesions because it lacks accessory disruptive effects and because of the sharp falloff in radiation of beta sources. BOYESEN & CAMPBELL have reported lesions resulting from yttrium 90 beads in the caudate nucleus of animals. However, we wished to create larger lesions of at least 1 cm in diameter from a single source. Also, it was necessary to examine the effects in the thalamus since there are regional differences in radiation sensitivity. These authors have expressed a sensitivity spectrum of the structures in this region which would be favorable for this type of energy. The order of sensitivity they found was that astrocytes were the most sensitive to radiation, next microglia, then neurons, and finally blood vessels and myelin are the most resistant. A question which arises is the possible carcinogenic nature of radiation. Long experience with external radiation therapy has failed to result in any verified case of glial tumor induction. Beta rays are believed to affect brain tissue by the common ionization in both of these methods. The risk seems small.

Macrospheres of 1.2 mm in diameter containing pure beta-emitting isotope yttrium 90 oxide are prepared by Brookhaven National Laboratory and shipped by air weekly to the University of California Medical Center in Los Angeles. The method of preparation has been described by GIVELL & DOERING. These beads are readily available, relatively inexpensive, and of sufficient activity to be usable for a number of days after delivery.

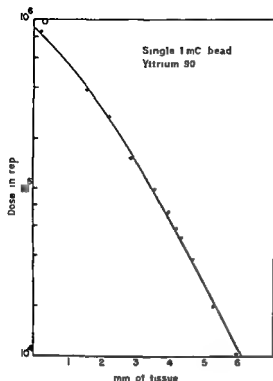


Fig 1. Film pack dosimetry curve for 1 mCi Yttrium 90 oxide bead calculated for 64 hours ( $T_{1/2}$ )

Yttrium 90 has a 54 days half life and a maximum energy of 2.18 MeV. Beta radiation has a limited range in tissue and hence there are no complicating features of distant effects. The low specific gravity of the ceramic matrix in which the yttrium is suspended raises the efficiency of delivery of the total dose as compared with dense metallic sources because of the lower self absorption. These yttrium 90 macrospheres are used in this medical center for transsphenoidal stereotaxic hypophysectomy as well as the procedure described in this article.

From previous experience in thalamic surgery for dyskinesia it has seemed evident to us that to achieve maximum benefit in relief of various involuntary movements, improvement in tone and in gait, that a spherical lesion of about 7 to 10 mm in diameter well placed in the nuclei ventro orales anterior and posterior of the thalamus is ideal. This conclu-

sion is mainly based on observations of patients with Parkinsonism but may be true of other disorders as well.

The structures critical to destroy permanently appear to be the nuclei ventro orales anterior and posterior of the thalamus. With the atlas of the human brain edited by SCHALTENBRAND & BAILEY as a guide, a hypothetical lesion was measured which would involve these nuclear complexes completely. A lesion placed at 12 mm from the midline in the center of these nuclei would have to be 1 cm in width, 1 cm in height and 1.2 cm in length. This volume would involve the thalamocapsular junction region which appears to be important to achieve a maximum beneficial effect. Portions of other nuclei would be partly involved, including nucleus ventro oralis internus, nucleus ventro intermedius internus, nucleus medianus.

The possibilities of yttrium 90 oxide spheres to involve such a volume was then investigated. The film pack method of FRIETAG et coll. was used for dosimetry studies. Dupont 555 film was employed, with paper spacer to simulate tissue density. These results reveal that radiation from a single 1 millicurie bead for a calculated time of 64 hours would give a dose of 10,000 rep at 6 mm.



Fig 2 Concentric ring stimulating the electrode in the thalamic nuclei

The abrupt falloff in dose rate as shown in Fig 1 is characteristic of beta emitters. This characteristic is ideal for producing a discrete lesion in tissue and the discreteness is further enhanced by the spherical shape and size of yttrium 90 beads. The size of the lesion can be varied according to the initial activity of the bead and the length of time it is left in place. The maximum penetration for yttrium 90 beta particles in tissue is 10 mm but beyond 6 mm a lethal tissue dose cannot be achieved because of marked absorption. Seventy per cent of the dose is delivered in 3 days. Therefore the rate of tissue destruction is considerably slower than by other methods and possibly allows collateral circulation to develop and produces less local edema.

### Preliminary study of lesions in animals

Twenty one mongrel dogs of medium size had implantation of a single yttrium 90 bead in each area under general anesthesia by the stereotaxic method of LIM, LIU & MOFFITT. The activity of the individual beads varied from 0.85 mCi to 1.9 mCi. The macrospheres were left in place for varying lengths of time up to 20 days. The age of lesions before sacrifice of the dog was varied up to 5 months. All figures quoted for the size of lesions have not been corrected for shrinkage of the formalin fixation.

In the first series of experiments the beads were implanted as free bodies in the brain tissue. Radiation activity of the sources varied from 1.5 to 1.9 mCi each. These animals each were sacrificed after anesthetization and formalin perfusion at intervals of 2 days, 6 days and 141 days, and two animals at 170

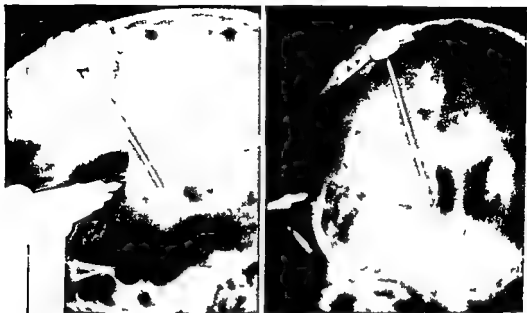


Fig. 3. Fixation bead holder and yttrium 90 oxide bead in the human thalamus

days. Lesions in the thalamus in these animals were found to be irregular, most commonly being pear shaped. This shape of the lesion was a result of 3 to 4 mm inferior migration of the bead. One animal with 3 beads inserted as a cluster in white matter had a migration of the cluster of 2.5 cm. An explanation of this process appears to be that beads of this activity produce a small zone of liquefaction necrosis in the immediate area. Edema or hemorrhage might also displace them. It was concluded that a fixation device for the bead is necessary to provide control of position and size of lesion.

Twelve animals were prepared using a loop cannula for fixation. Two small wire loops soldered into No. 18 stainless steel tubing provided a carrier for the yttrium bead, and this complex was fixed by a plastic plate screwed into the calvarium. The plastic plate was drilled and the loop cannula securely fixed into its perforation with Kadon<sup>®</sup> and then the protruding end above the surface severed. The scalp was closed over this.

In this series of animals the bead activity varied from 0.9 to 1.5 mCi. The animals were divided into two groups, group A to show the histologic reaction up to 20 days, group B to show chronic lesions at 3 to 6 months. Group A consisted of 3 animals in which the extent of the acute reaction was studied as a result of the bead being in place 1 day, 6 days, 20 days ( $\pm 3$  hours). In group B of 9 animals with chronic lesions, the bead remained for a duration of 1, 2, 3, 5, 8, 12 days ( $\pm 3$  hours).

Regardless of the radiation activity of a bead or its duration in place in the various phases of development of histologic changes in the lesions, it was found that the maximum swelling was at 20 days and thereafter there was a contraction of the lesion into gliosis. When the bead was fixed in this manner any lesion in the area of absolute destruction was spherical. Because of the decay in activity of yttrium, leaving the bead in place after 6 days does not increase the volume of the lesion.

After a lesion has aged more than 20 days it becomes progressively smaller and more irregular in configuration because of shrinkage and gliosis; however, the absolute destruction of the thalamic nuclear groups remains the same.

The maximum volume of complete destruction produced by any fixed yttrium 90 bead used and at greatest duration in place was a spherical lesion of 12 mm in diameter. Fixed beads will produce circumscribed spherical lesions showing a small zone of coagulation necrosis, a ring of capillary diapedesis, and a small irregular zone of edema and partial damage. Smaller lesions can be produced by shortening the duration of time that the bead is in place or by employing a bead of less activity.

The histologic changes of a maximum lesion at 20 days are illustrated as an example. In this lesion if we consider that it has a radius from the central point there is a zone 4 to 5 mm wide in which there are varying degrees of necrotic liquefaction, coagulation necrosis, and fibrin. A few intact neurons and astrocytic nuclei may be seen even toward the center of the lesion but they do not appear viable. Some polymorphonuclear, mononuclear, and lymphocytic cells are seen as well as some gutter cells. Around this there is a striking ring about 1 to 1.5 mm wide of a layer of diapedesis of red cells, necrosis, hyaline degeneration of the media and intima of blood vessels. Outside this ring there is a fairly sharply defined rim 1 to 1.5 mm wide, characterized by the presence of blood vessels with proliferated intima and marked infiltration.

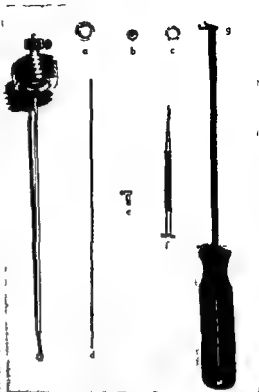


Fig. 4. The assembled fixation apparatus is seen to the left: a) Threaded cylinder to be screwed into a 8 mm burr hole; b) Perforated metallic ball; c) Fixation ring; d) Stainless steel bead holder; e) Set screw collar; f) Jeweler's screw driver; g) Screw driver for fixation on ring.

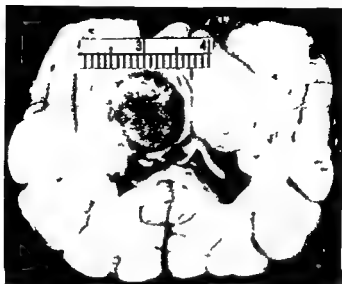


Fig 5 Lesion produced by an yttrium 90 oxide bead of 1.4 mC activity left in place in the thalamus of the dog for 6 days. The dog was sacrificed at 14 days to show the early reaction.

of inflammatory cells. In the remaining periphery, small pseudopods of irregular shape and representative of edema are seen. The edema causes some diminution in the size of the ventricular cavity but not enough to cause a shift even in the small brain of the dog. More extensive exposition of the quantitative effects and the histologic reactions will be published in the near future.

### Clinical application

Since October 1960, 13 patients with dyskinesia have had yttrium 90 thalamotomy. Eleven patients suffered from either post encephalitic Parkinsonism or paralysis agitans. 2 patients had dystonia musculorum deformans and one had post traumatic cerebellar tremor disorder. Patients selected for this operation were in general severely disabled and by current standards generally used, were considered either borderline or ineligible for the cr devant alcohol injection (COOPER & BRAVO) treatment used at this institution. It was hoped that these radiation lesions, being highly circumscribed and controllable in size by withdrawal of the bead, would assist in rehabilitating a borderline group of cases as well as to give an evaluation of this form of treatment.

*Surgical procedure* Anatomical landmarks to locate the site of the lesion are delineated by an encephalogram during which the patient's head is fixed in a Lee model 215 head and cassette holder. In some instances in which the



Fig 6 Histologic preparation of a lesion at 14 days 125 mCi yttrium 90 oxide macrosphere left in place for 6 days

posterior part of the third ventricle was not satisfactorily seen a small amount of Pantopaque<sup>®</sup> was injected via a small catheter directed to the foramen of Monro. The ventricular landmarks have been the posterior margin of the foramen of Monro the anterior and posterior commissures the habenular commissure and the pineal body. In lateral roentgenograms proportions were used consisting of mid foraminal pineal line (COOPER & BRAVO) and mid antero posterior commissure axis with mid thalamic height (TALAIRACH et coll). Our tube film distances were 36 inches giving an enlargement factor of approximately 20 % for antero-posterior and 10 % for lateral views. In the antero posterior films the corrected distance from the midline third ventricle was 12 mm however in cases of atrophy it was altered further laterally. References used for landmarks were the human atlas of TALAIRACH et coll, and SCHALTENBRAND & BAILEY. Permanent and polaroid films have been employed. The Rand Wells stereotaxic instrument with sagittal and coronal arcs was used to direct the electrode and cannula.

Further identification of the nucleus ventralis lateralis of the thalamus by electrophysiological means as well as these anatomical landmarks is important. This anatomical precaution is necessary because of the normal variations of these structures variations from pathological alterations and variations even from side to side in the same patient as has been well documented by BRIERLY & BECK.

After a 10 mm burr hole has been made 3.5 cm from the midline at the level of the coronal suture the dura mater and cortical surface at the site are opened. A tap is used to create threads in the burr hole to accept a small ball and a socket fixation device used later to fix the yttrium cannula. With the stereotaxic device a Talairach multiple concentric ring electrode is then lowered to the anatomical target. Sterile scalp as well as electromyographic electrodes in the limb muscles are then applied to the patient. Stimuli are delivered to the depth electrode with a Grass 4S type stimulator with isolation unit. Single or repetitive trains of square wave form stimuli with parameters varying from





Fig. 7 Irregularly shaped lesions seen at 7 days produced by 0.95 mC activity and without fixation of the macrospheres

1 to 50 cps duration 1 msec for low frequency and 0.5 msec for high frequency. The voltage and duration of stimulation have varied from 3 to 15 volts, and 5 to 10 seconds respectively, depending on responses seen in the electroencephalogram monitoring oscilloscopes and the alert patient. The electrophysiological responses identifying this area have been reported by RAND and GRANDALL. In short they consist of (1) suppression or augmentation of tremor and rigidity, (2) correlation of electrophysiologic recordings of such phenomena as recruitment and evoked potentials with tremor suppression or augmentation as shown in the electroencephalogram, cathode ray kymograph, and electromyogram. The involuntary movements that may be augmented by stimulation are always of the same type as the patient displays spontaneously. We have never seen a change to a different involuntary movement other than the characteristic clonic jerks seen with internal capsule stimulation. In 2 cases we were unable to elicit these responses, in these instances a temporary mechanical compression in the anatomical area was made by an inflation of the balloon on a Cooper cannula and the patient was tested for the effect.

After the surgical target is located by these means the depth electrode is withdrawn, and the ball within the ball and socket device is locked in the correct angle. The yttrium 90 bead is delivered in a plastic container from the division of radiotherapy where its activity has been calculated and it has been handled with sterile precautions. The bead itself is kept under 3 cm of sterile water during the loading of the carrier loop. After loading radiation precautions are observed, and the surgeon quickly transfers the loaded carrier to the stereotaxic device and lowers it to the target. A small collar allows the

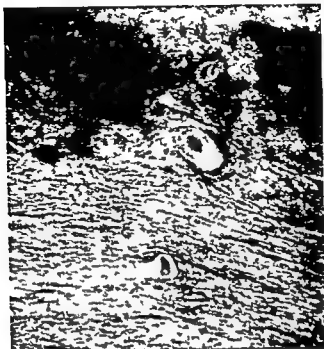


Fig 8 Histologic preparation of rim of a spherical lesion at 14 days showing the coagulation necrosis above next the diapedesis of red cells and the surrounding white matter below H & E stain

carrier rod to be screwed into the top of the ball and another small screw tightens the collar to the rod. When its position has been judged to be correct on roentgen films and the apparatus is completely secured the protruding portion of the carrier rod is clipped flush with the collar. The scalp is then closed over the entire device. Stainless steel sutures over polyethylene tubing are used for a through and through closure and secured by twisting.

The bead is left in place for a variable length of time depending on the size of the lesion desired. We have usually observed that the alleviation of tremor and rigidity in successful cases gradually proceeds until the total effect is evident on the third day. When the yttrium 90 bead is to be removed the procedure is carried out in the ward treatment room. With aseptic precautions the wire sutures are loosened, the cannula removed, and the ball and socket fixation device removed with the tools shown in Fig 3. The bead, kept in fluid in a small glass bottle, is returned to the radio therapy department. The scalp is reclosed by retwisting the steel wires.

There are no problems in postoperative nursing care in regard to radiation safety precautions. The head of such a patient has been monitored and the bremsstrahlung, at surface level, has been found to measure less than one and a half times the background level.

### Clinical results

This particular group of patients is small in number, and in such a poor risk category as not to be comparable with other series. The results are regarded by us as favorable. The effects which should be gained in the treatment of Parkinsonism and paralysis agitans are better known than most other dyskinesias. In the 9 patients with follow up periods of 4 to 11 months there were 6 who had excellent results. This signifies that the patients regained normal motor performance in the affected limbs and relief of rigidity, tremor, and bradykinesia. There was one patient who had incomplete relief. Two poor results occurred: one because of aggravation of a pre-existing poor mental status, and another because of accidental displacement of the yttrium beads.

It is concluded that an excellent result can be obtained by such a technique. It is also noteworthy that not one instance of stupor, coma or akinetic mutism occurred in the immediate postoperative course. There were no instances of hemiplegia which is usually a complication due to hemorrhage. Immediate postoperative side effects, which did occur, consisted of transient confusion, slurred speech, transient hemichorea which usually means partial involvement of the subthalamic nucleus. Hypophonia as a late sequel was seen in two patients. Hemichorea can perhaps be avoided by 5 mm retraction of the bead when the first sign appears.

In order to gain a true evaluation of this kind of operative treatment it will be necessary to carry it out on a large number of patients. The present trend, indicated to us in these patients, is however that the lesion can bring about an excellent response, with a freedom from the side effects that often occur as a result of edema and swelling.

### SUMMARY

A technique for thalamotomy employing yttrium 90 macrospheres was used in the treatment of Parkinsonism, paralysis agitans, dystonia musculorum deformans and cerebellar tremor. By utilizing the physical characteristics of beta emitters to achieve a circumscribed complete lesion, physical disruptive effects are avoided. The crucial target, the ventrolateral nucleus, is subtended by a 1 cm diameter spherical lesion. Animal experiments have shown that fixation of the source is necessary to avoid migration of the bead. Twelve patients were treated. Observation of the patients from 4 to 11 months has shown that an excellent result can be achieved with few or no side effects.

## ZUSAMMENFASSUNG

Eine Technik der Thalamotomie mit Yttrium 90 wurde bei der Behandlung von Parkinsonismus, paralysis agitans, dystonia musculorum deformans und cerebellarem Tremor angewendet. Bei Auswertung der physikalischen Charakteristika von Betastrahlern beim Erzeugen von umschriebenen Gewebszerstörungen konnten störende physikalische Nebeneffekte vermieden werden. Eine Gewebsablation von 1 cm Durchmesser deckt das zu bestrahlende Gebiet des ventrolateralen Nucleus. Tierexperimente haben gezeigt, dass die Fixierung der Strahlenquelle nötig ist, um Verschiebungen der Perle zu vermeiden. Zwölf Patienten wurden behandelt. Eine Nachbeobachtung der Patienten über 4 bis 11 Monate hat gezeigt, dass ausgezeichnete Resultate mit nur geringen oder gar keinen Nebenwirkungen erzielt werden können.

## RÉSUMÉ

Les auteurs ont utilisé une technique de thalamotomie au moyen de sphères d'yttrium 90 pour le traitement de la maladie de Parkinson et des syndromes parkinsoniens de la dystonie musculaire déformante (spasmes de torsion, maladie de Ziehen, Oppenheim) et des tremblements cérébelleux. On peut éviter des effets physiques excessifs en utilisant les caractéristiques physiques des émetteurs bêta pour obtenir une lésion complète circonscrite. La cible qu'il importe d'atteindre, le noyau ventral latéral, est contenue dans une lésion sphérique d'un cm de diamètre. L'expérimentation animale a montré qu'il est nécessaire de fixer la source de radiation pour éviter la migration de la perle. Douze malades ont été ainsi traités et suivis pendant une période de 4 à 11 mois. On a constaté qu'on peut obtenir un excellent résultat avec des effets secondaires minimes ou nuls.

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## HEMANGIOBLASTOMA CEREBELLI — REPORT OF A SIX YEAR SURVIVAL AFTER ROENTGEN THERAPY BY TUMOR OSCILLATION THROUGH A GRID

by

HIRSCH MARKS

The incidence of blood vessel tumors comprised only 2 per cent of the total of CUSHING's 2 033 verified intracranial tumors. Although not exclusively characteristic of the brain these tumors are relatively important in neuro pathology. They may be divided into congenital anomalies and true neoplasms. Congenital anomalies usually occur as either venous or arterial malformations. These malformations give rise to symptoms resembling those of a brain tumor. The reason for these symptoms is usually the size and increased vascularity of the congenital anomalies. The venous malformations consist of thin walled large venous vessels the arterial ones of tortuous arteries. Degenerated brain tissue is often found between the vessels. Sometimes recognition of parallel streaks of calcification within the walls of such anomalous vessels, in the conventional skull films is of help to the clinician.

Hemangioblastomas are tumors usually of middle life. They typify the true neoplasms originating from blood vessels and occur, most commonly within the cerebellum. These tumors are brownish in color on their cut surface and show microscopically lacunae with richly cellular tissue in between. The cells

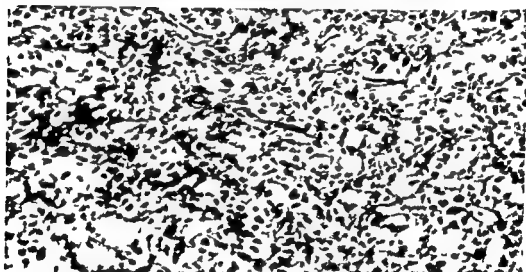
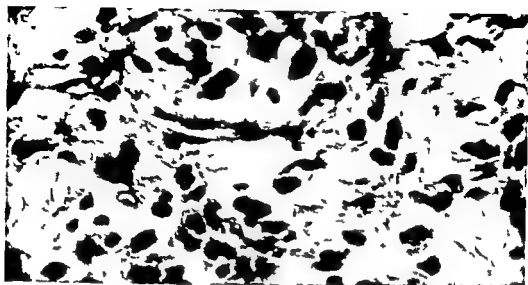


Fig 1 Fat globules suggestive of xanthoma cells may be observed in hemangioblastoma when fat stains are applied

have large oval nuclei with evenly distributed chromatin. Fat globules suggestive of xanthoma cells may be observed when fat stains are applied (Fig 1).

Hemangioblastomas are most commonly seen as single lesions. They are occasionally associated with angiomatous malformations of the retinae (Von Hippel's disease) or cyst of liver, kidney, ovaries, pancreas, etc. The combination of hemangioblastoma of the cerebellum with one or more anomalies in one patient, often familial in nature, is known as Lindau's disease (DAVIDOFF & EPSTEIN).

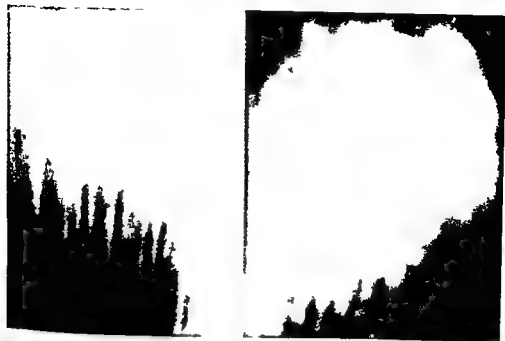


Fig. 2 Absorption patterns in pendulum grid therapy

**Case report.** Female, age 35 years. Two years before admission she first became aware of pain in the right side of her head which grew progressively in intensity and extent spreading to the eyes and face. Recently the headaches were accompanied by vertigo, nausea, vomiting independent of food intake, and on one occasion terminated in loss of consciousness and convulsions. The past history revealed hysterectomy at the age of 20 years for excessive bleeding and asthma at the age of 16 years.

On neurological examination the patient was seen swaying with eyes open, considerable tremor of head, ataxic gait with falling to the right side, and tremor of the right hand on voluntary movement, enunciation with irregular force and rapidity. Ophthalmoscopic examination revealed blurred vision, nystagmus, and bilateral papilledema; retinal veins were dilated and tortuous, the arteries were constricted, and all vessels were broken off at the margins of the disks. Spinal fluid studies elicited the following: pressure 380 mm of water, glucose 80 mg/100 ml, chlorides 720 mg/100 ml, protein 52 mg/100 ml.

Ventriculography showed marked symmetrical dilatation of both lateral ventricles as well as of the third ventricle with no evident displacement.

**Operative findings (Schenkman).** A reddish blue mass was seen separating the cerebellar hemispheres; it was hard to determine whether this mass was entirely within the fourth ventricle or was arising from the edge of the right cerebellar hemisphere. Extreme vascularity prevented the resection of the mass. Several small biopsy specimens were obtained from this tissue. The gross description of the pathologic report (Dolgopolsky) specimen consisted of 4 small fragments of spongy grayish white tissue; gross section revealed some grayish brown areas. The microscopic description was: Malignant hemangioendothelioma.





Fig. 3 Case of hemangioblastoma of cerebellum. No epilation after 4 000 r in air by rotation through a grid 10  $\times$  15 cm. absence of any depilatory reaction of the scalp.

### Treatment

Roentgen therapy with the use of a grid was instituted by tumor oscillation in an angle of 180° through the sub occipital region. The radiation was of quality 1.6 mm Cu HVL, 50 cm STD, 250 kV, grid size 10  $\times$  15 cm with apertures of 0.5 cm in diameter and of an area ratio of 40 % translucent and 60 % opaque. The daily dose was 200 r in air. The total dose, assessed by the gradual disappearance of the clinical symptoms, was reached at 4 000 r in air, and was administered in 20 treatment days, in an overall period of 4 weeks and 4 days.

The constant presence and vigilance of the attending radiotherapist are the condition sine qua non of the clinical method of treatment. With the symptoms, and not an a priori dose, as the guideposts, one is compelled to discontinue the treatment once the symptoms have attained their vanishing point. Some slight symptoms may persist for a while after completion of the treatments. However, when they continue unabated, as was the case with our patients, additional treatment must be administered. The latter, 1 400 r in air, was delivered with the same factors as above in daily doses of 200 r in air, in an overall period of 12 days. *Citrus bioflavonoid compound with ascorbic acid*, 1 500 mg daily, was administered as adjuvant therapy.

### Comments

The skin reaction to roentgen irradiation through a grid in rotation is reduced to a minimum and is lowest in anatomical sites approximating a cylindrical configuration.

This observation was gleaned from clinical experience about 9 years ago (MARKS 1953, 1954, 1955), at a first attempt at irradiation, by tumor oscillation through a grid, of a patient in extremis. This patient had been previously

treated to skin tolerance and returned to work. One year later an emergency tracheotomy was performed for a diffusely growing and rapidly expanding carcinoma of the laryngo pharynx with circular metastases to the neck. The ensuing total lysis of the malignant process with no concomitant skin reaction except erythema served as a powerful incentive to spur the author on the apply irradiation by tumor oscillation through a grid is the method of choice in all patients for whom encompassing the growth daily was an imperative.

This method effectively impedes spread of the growth without the dreaded stress of local and generalized systemic reaction. That these reactions were obviated was largely due to the recovery factors inherent in the unirradiated spaces as well as to the higher ratio of tumor to integral dose absorption afforded by this method.

The higher ratio of absorption is brought to fruition in the following manner: the primary energy impulses emanating from row upon row of grid apertures — upon leaving, on the surface film of the masonite phantom the imprint of a grill (Fig 2), and on the succeeding films beneath it a latticework imprint (Fig 2) — continue to pursue their paths in the form of a ripple (Fig 2) around the oscillating tumor in the depth. The primary energies along with their secondaries are, therefore, diverted away from the periphery toward the revolving tumor center, and the normal tissues outside the irradiated field are consequently relieved of the stress of secondary radiation.

Thus a physical therapeutic agent roentgen rays — bedevilled by many side effects of a local and general character which render it impossible of application in tumors of large volume — was converted by oscillation through a grid to a therapeutic agent par excellence, akin in its effectiveness to the organ affinity or tropism of a chemical agent.

### Acknowledgements

I acknowledge with appreciation and gratitude the kind assistance of Miss Shirley Johnson radiation and isotope technician, Miss Victoria Hirschfeld secretary, Miss Volda Whittaker and Miss Maria Burton radiation technician.

### SUMMARY

A case of unresectable hemangioblastoma of the cerebellum was treated by oscillation through a grid with 250 electronkilovolts. The patient has been symptom free for the past 6 years. There was increased selective localization of the radiation energy in the tumor proper and very little in the skin of the scalp.

### ZUSAMMENFASSUNG

Ein Fall mit einem nicht resezierbarem Hamangioblastom des Kleinhirns wurde mit 250 Kiloeltronvolt mittels Oscillation unter Verwendung von einem Raster behandelt. Der Patient ist seit 6 Jahren symptomfrei. Durch diese Technik wurde eine erhöhte selektive Lokalisierung der Bestrahlungsenergie im eigentlichen Tumor erhalten, weil die Hautbestrahlung nur gering war.

## RÉSUMÉ

Un cas d'hémangioblastome inextirpable du cervelet a été traité par roentgenthérapie pendulaire avec grille sous 250 kV. Le malade a survécu sans symptômes ces six dernières années. La localisation sélective de la dose d'irradiation a été très augmentée au niveau de la tumeur et très faible sur le cuir chevelu.

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## IONIZING RADIATIONS AND THE MAMMALIAN EMBRYO

by

ROBERTS RUGH

When considering the biologic effects of ionizing radiations one must never confuse the embryo with the adult into which that embryo develops (RUGH 1962) The reactions of the two are totally different both in degree and in quality Every stage of embryonic or fetal development is more radiosensitive than is the post natal organism by any test applied Lethality is greatest in the early stages just after fertilization, but congenital anomalies occur more frequently following roentgen irradiation at a later stage (RUGH 1959 1961, 1962 RUGH & GRUPP 1959) Still later just before birth neither lethality nor congenital effects are seen but the fetus responds by developing functional sequelae which may not be fully manifest for some years Also it must be remembered after about 5 months for the human the gonads develop and contain primitive germ cells which are themselves very radiosensitive and these cells not only accumulate the damaging effects of radiations in terms of genic mutations but pass them along unaltered to their progeny

When we realize that the embryo and fetus are so radiosensitive we tend to forget that in ionizing radiations we are dealing with a physical entity

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Fig 1 a) Mouse egg at moment of invasion by spermatozoon in the process of fertilization. Roentgen irradiation at this time is essentially like that of exposure of both gametes separately. This stage is very susceptible to roentgen irradiation effects usually resulting in death. b) Effect of roentgen irradiation on zygote shortly before approximation of male and female pronuclei. Hyperchromaticity of male pronucleus has resulted from 15 r exposure.



Fig 2 Upper oviduct of mouse showing four recently fertilized eggs shortly after mating.

that is most powerful. An exposure which ionizes 1 molecule in 10 million (1 000 r) will kill most adult mammals, and an exposure which ionizes only 1 molecule in 1 000 million molecules (10 r) will cause lymphopenia in the adult and chromosome aberrations and congenital anomalies in the embryo. Thus, in contrast with the adult, the embryo and fetus are much more radiosensitive with respect to ionizing radiations which are extremely potent.

It has been known for some time that roentgen irradiation of the mammalian embryo at the beginning of neurogenesis will cause the highest percentage of gross CNS anomalies (Hicks et coll 1952, 1953, 1954, 1959). This period is about 7.5 to 9.5 days for the rodent (mouse or rat) and about 18 to 25 days for the human. It is likely that any trauma would have a maximum effect in producing these anomalies at such a time, but ionizing radiations are so penetrating so instantaneous in their impact that as many as 48 % of the



Fig 3 a) Fragmentation of fertilized egg by 15 r exposure at the stage seen in fig 2. Pieces of cytoplasm are pinched off but both pronuclei remain in the larger fragment of cytoplasm. b) Complete fragmentation of zygote from 15 r exposure. c) Exposed zygote pinching off cytoplasm but this time the pronuclei are contained within the discarded material. The remaining cytoplasmic mass without either nuclear component could not survive. While 15 r can cause these effects their occurrence is statistically low.

mouse embryos exposed at 8.5 days will develop the severe cerebral anomaly known as exencephaly or brain hernia (RUGH & GRUPP 1959, 1961, 1962).

Following the completion of organogenesis it is impossible to produce gross congenital anomalies by means of ionizing radiations. Some anomalies can indeed be caused but they affect the cytoarchitecture of the brain on an histologic level. It is now believed that levels of exposure much lower than the 200 r referred to will elicit functional effects not always manifest at birth. In fact there is evidence that behaviour effects evident through electroencephalography and possibly other mental disturbances may follow by years the exposure, even at low levels, of the late fetus.

Prior to the onset of neurogenesis at about 7.5 days in the mouse embryo it had long been assumed that congenital sequelae could not be elicited by ionizing radiations (RUSSELL 1950, 1956, 1957; RUSSELL & RUSSELL 1956). This was because rather high levels of irradiation were used so that most of the early embryos were killed. It is the surviving but damaged embryo that shows the congenital anomaly so that a dose which kills off the majority of early embryos would be one to actually reduce the incidence of congenital anomalies.

Recently it has been demonstrated that exposures of as little as 10 r to the mouse embryo in the 2 cell stage can cause the development of exencephalia or the cerebral hernia. True it does not occur in great frequency but the fact that it occurs at all in a strain of mice where it had never before been seen among the controls suggests that possibly even 10 r is not the threshold dose for congenital effects. (This anomaly has recently been seen among non irradiated controls the frequency being 3 in 1000 control embryos.)

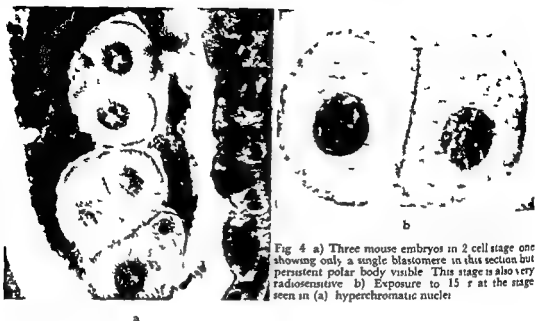


Fig 4 a) Three mouse embryos in 2 cell stage one showing only a single blastomere in this section but persistent polar body visible. This stage is also very radiosensitive. b) Exposure to 15 r at the stage seen in (a) hyperchromatic nuclei.

Exencephalia brain hernia is a developmental defect which prevents the closure of the neural folds at the mid brain level, so that the cranial roof does not form properly and the brain protrudes through the skull roof. This and the related anencephaly occur at a rate of about 1 in 500 cases of human births, but can be produced regularly in rodent embryos by roentgen irradiation at certain times. Whether background or even extended diagnostic irradiation might be the cause of this anomaly in human births is, at this time, still conjecture. However, it must be suggested that the human embryo is probably substantially like the rodent embryo in regard to radiosensitivity, and while we cannot extrapolate from the rodent to man, we should take rodent data as suggestive.

The above statements have been made on the basis of findings with over 60 000 mouse embryos and fetuses, examined shortly before and after birth. It so happens that the mouse, producing congenitally abnormal newborn will kill and devour them immediately so that it is necessary, in order to obtain reliable statistical data, to study most of these fetuses just before the time of expected birth.

Current studies are directed toward a further understanding of the relation of embryonic or fetal exposure and a large variety of congenital anomalies. However, it seems quite definite that the studies will have to be directed to the levels of electron microscopy for structural effects and to the electroencephalogram, the electroretinogram, and standard behaviour tests, to determine

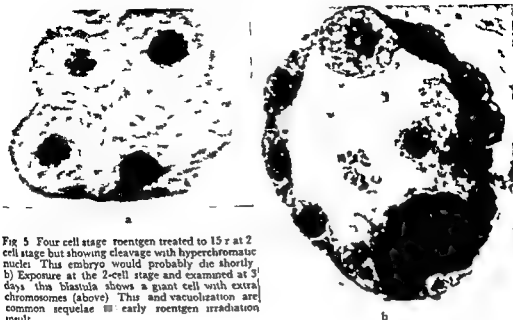
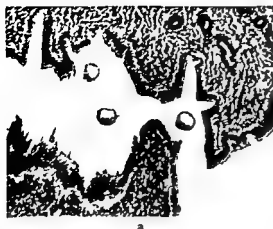


Fig 5 Four cell stage roentgen treated to 15 r at 2 cell stage but showing cleavage with hyperchromatic nuclei. This embryo would probably die shortly. b) Exposure at the 2-cell stage and examined at 5 days this blastula shows a giant cell with extra chromosomes (above). This and vacuolization are common sequelae of early roentgen irradiation insult.

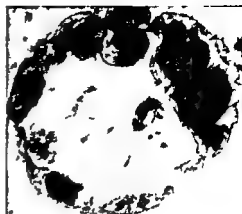
effects not seen by histopathology. Further, we are forced to lower the exposure level and are currently studying the effect of 1, 5, and 10 r single exposure at each and every 24 hour period from fertilization to 18.5 days gestation. Embryos and fetuses thus exposed are being analyzed for immediate effects as well as those long term sequelae such as sterility, leukemia, cataracts, ageing, and the incidence of a variety of tumors.

Diagnostic radiology is as essential to medical practice as the scalpel is to the surgeon. Ionizing radiations, used for peaceful purposes, have and will advance civilization more rapidly than any other single physical aid known to man. Therapeutic levels of roentgen irradiation are saving the lives of thousands by treatments every day. Thus, there is no justification in condemning ionizing radiations upon the realization that they can be so devastating to the embryo and fetus. Rather, the clinician should be informed of these findings and urged to protect the gravid uterus in all instances of pelvic irradiation. Further, since the human embryo is probably most radiosensitive at a time when a pregnancy is least suspected, namely between 15–42 days after the onset of menstruation, it is rapidly becoming an accepted practice to limit extensive radiodiagnosis of the female pelvis to the first 9 days following the onset of menstruation in order to avoid the earliest stages of an unsuspected pregnancy. In this way we may eventually reduce the 5% incidence of congenital anomalies expected in human births.





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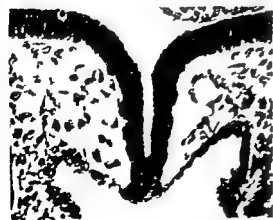
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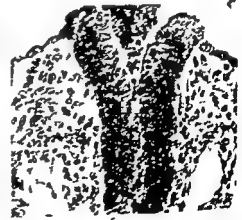
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e



f

Fig 6 For legend see opposite page



Fig 7 When mouse embryos are exposed at 35 days (Cf fig 6a) to 50 r and survive they may develop these severe cephalic anomalies found in the sole survivors of a single litter. The damage appears to be largely of the CNS and anterior although there are always some internal anomalies such as of the kidney heart etc. Such individuals could not survive.

Legend to Fig 8 a) Three blastula suspended within the uterine lumen at 35 days after copulation in the mouse. These would be expected to implant within 24 hours and are highly radiosensitive. b) Blastula exposed to roentgen rays showing vacuolization of some cells (above). c) Roentgen irradiation at the blastula stage (shown in a) but allowed to develop to time of implantation (shown in d) and accumulation within the blastocoel of loose cells which have been discarded by this early embryo. If such an embryo should survive and develop it would be deficient to the extent of these discarded cells proportionately to the total number of cells of the blastula. d) Normal implantation at 45 days after copulation. e) Neural groove at 73 days development when there is abundant neuroectoderm being transformed into neuroblast which are extremely radiosensitive. If exposed to roentgen rays in excess of 25 and examined within 24 hours it can be seen that many of the sensitive cells have been killed (see next view). f) Neural groove 74 hours after roentgen irradiation showing many pyknotic cells and many being sloughed off into the exterior of the embryo. Survival would result in a neural deficient embryo and fetus.

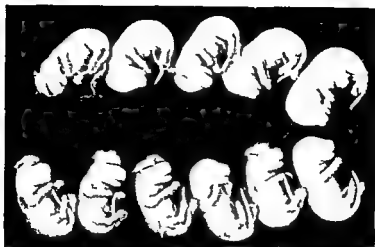


Fig 8 An entire litter as found in the bicornuate uterus of the mouse at 18.5 days showing 5 out of 11 members with the extreme cerebral anomaly known as exencephalia or brain hernia. This was due to exposure to 200 r at 8.5 days of development when the neuroblasts of the CNS were most abundant.

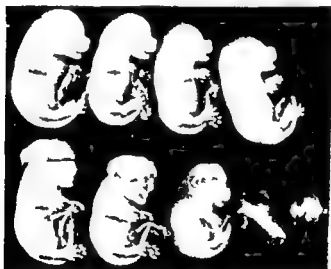


Fig 9 Heterozygosity is a protective variable for a litter of mice known as heterosis, but this does not apply to the embryo. This is a litter of hybrid mice (C3H  $\times$  C57) exposed at 8.5 days to 200 r showing a variety of anomalies from minor stunting (upper left) to death and resorption (lower right). Intermediate effects are exencephaly and gross stunting.



Fig 10 One instance of hereditary exencephalia caused by exposing the female mouse to 100 r and breeding her to a normal male. This anomaly appeared in three successive generations though infrequently therefore genetic.



Fig 11 Enlarged view of exencephalic brain hernia due to interruption of development of the brain and the covering cranial roof. The balance of the head including the eye appears to be rather normal.

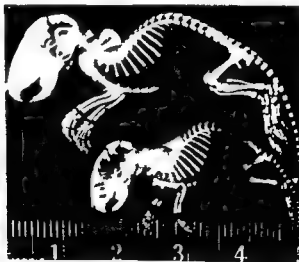


Fig 12 Roentgen views of the skeleton at birth of a normal (above) and a fetally x-ray irradiated (below) mouse skeleton showing that there is topographical normality though extreme stunting in the exposed mouse. This is due to cell loss at an early stage the remaining cells being utilized by the embryo as a whole to develop a well balanced though reduced individual.

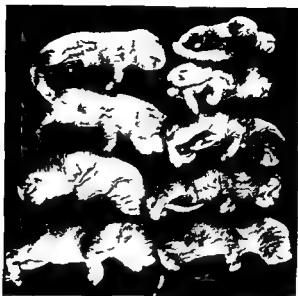


Fig. 13 An entire litter of rats at birth following exposure to 100 r at 95 days embryonic development. The great variety of anomalies occurring within the single litter exposed to identical roentgen irradiation is notable.



Fig. 14 Enlarged view of few members of litter seen in fig. 13 to show gross anomalies largely involving the central nervous system.

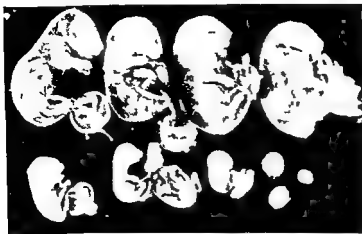


Fig 15 Entire litter of rat embryos just before time for delivery showing death and resorption of three dead fetuses also three in number and the remaining fetuses reduced but still to look more like mouse embryos

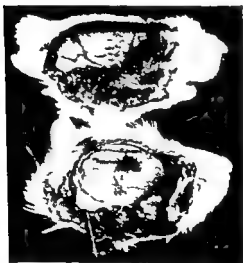


Fig 16 Hemisected skulls of two rats at 2 weeks of age showing (above) control with normal brain and (below) roentgen irradiated to 100 r in utero at 95 days showing collapsed brain of hydrocephalus and visual



Fig 17 Gross sections (transverse) of brains of rats at 2 months of age. The single control to the left and other five are members of a single litter showing various degrees of hydrocephalus.



Fig 18 Control to the left and two brains of hydrocephalic rats treated by 100 r at 9.5 days gestation. These roentgen irradiated brains are also grossly distorted.

## SUMMARY

It has been found that the mammalian embryo shows varying reactions to ionizing radiations such that it is always more radiosensitive than is the adult into which it develops. At some stages 100 times as sensitive. After neurogenesis is completed, congenital anomalies of that system are rarely produced, but exencephaly (brain hernia) has been caused by ionizing radiations impinging upon the 2 cell stage of the mouse with an exposure of as little as 10 r.

## ZUSAMMENFASSUNG

Es wurde gefunden, dass der Säugetierembryo gegenüber ionisierter Strahlung verschiedenartige Reaktionen zeigt. So ist er ca. 100 mal strahlenempfindlicher als das erwachsene Muttertier. Das den Embryo in sich tragende vollzogene Neurogenese und congenitalen Missbildungen des Nervensystems selten. Jedoch konnte mit so einer geringen Dosis ionisierter Strahlung wie 10 r im 2. Zellstadium bei der Maus Exencephalie (zerebrale Hernienbildung) verursacht werden.

## RESUMÉ

On a constaté que les embryons de mammifères ont des réactions variables aux radiations ionisantes et sont toujours plus radiosensibles que l'adulte dans lequel ils se développent. A certains stades 100 fois plus sensibles. Quand la neurogenèse est terminée les anomalies du système nerveux surviennent rarement, mais l'exencephalie (hernie cérébrale) a été provoquée par des radiations ionisantes au stade de 2 cellules chez la souris avec des doses ne dépassant pas 10 r.

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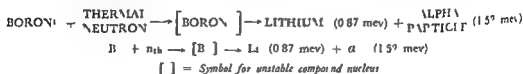


## BORON-SLOW NEUTRON CAPTURE THERAPY OF GLIOMAS

by

W H SWEET A H SOLOWAY and G L BROWNELL

The type of radiation following capture of slow neutrons presents a possible method for destroying tumor rootlets which remain after surgical extirpation of cerebral neoplasms



When the isotope boron 10 captures a slow neutron the ensuing compound nucleus disintegrates at once into a lithium atom and an alpha particle. These share between them the huge energy, 2.4 million electron volts which is also evolved. But because of the relatively enormous size of the particles they travel only about 8 microns in tissue. Hence the destruction they cause is confined to the site of the disintegrating atom. The greater the concentration of boron 10 in tumor than in brain the greater the differential injury to the tumor.

During the last 11 years 140 boron compounds have been studied by SOLOWAY (1, 2, 4, 5, 6) in mice, bearing gliomas re the differential tendency of the compounds to enter the tumors and in larger animals as well for their toxicity.

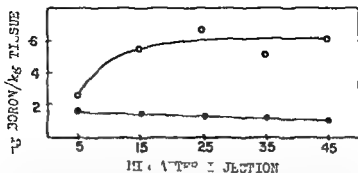


Fig 1 Boron concentration in man intravenous injection of 3 mg/kg p-carboxyphenylboronic acid. The curve marked with empty circles represents 17 biopsies in 7 patients with glioblastoma. The curve marked with filled circles represents 13 biopsies in 6 patients with normal brain.

The 6 most favorable of these have then been given intravenously in small doses to patients while they were undergoing craniotomy for tumor. The tumor and any normal brain necessarily removed with it were assayed for boron. Fig 1 is a plot of boron concentration against time for glioblastoma and for normal brain in man when the compound given was paracarboxybenzene boronic acid. The tumor to brain ratio 15 to 45 minutes after injection rises slowly from 3 to 1 up to 5 to 1.

DE ROUGE-MONT and SOLOWAY have demonstrated that the barrier mechanism between blood and normal brain in the dog recovers from the insult of cerebral lobectomy within three weeks.

Hence we seek in our patients to carry out the irradiation from the boron slow neutron capture 2 to 3 weeks after the grossly total resection of the tumor. The original wound is completely re-opened in a special operating theatre (Fig 2) beneath the core of the nuclear reactor of the Massachusetts Institute of Technology. Scalp muscle and bone which like tumor take up much boron are widely reflected in order to minimize radiation injury to them (Figs 3 and 4). We place thin gold foils on cerebral surfaces and tiny gold wires into the depths of the brain.

Following the irradiation we measure from the radioactivity induced in the gold the slow neutron dose. From these analyses and those for boron uptake obtained at the first operation on each patient we arrive at a first approximation of the dose due to heavy particles. Moreover since the slow neutrons penetrate matter poorly we also remove the cerebrospinal fluid at the lobectomy site and if necessary replace it by an air filled balloon. A tube to the bottom of the field is connected to suction for preventing accumulation of cerebrospinal fluid during the 30 to 105 minute period of irradiation. The patient is elevated to the ceiling portal, we leave the room but give anesthesia and check the vital signs from the adjoining area outside the concrete shield.

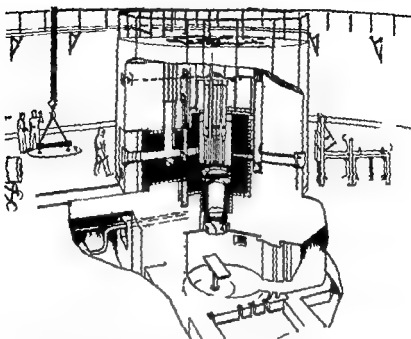


Fig. 2. Cut away diagram of MIT nuclear reactor. The operating room is directly below the core of the reactor. A hydraulic lift on the operating table permits elevation of the patient to the ceiling when the wound has been opened. Shutters above the ceiling portal in the operating room are independently controllable so that all other reactor studies proceed without interference.

Between mid November 1960 and mid August 1961 we irradiated 16 patients after intravenous injection of paracarboxybenzeneboronic acid made with boron 10. Eight of these have already died from 2 to 6 months after irradiation and the post mortem material from 7 of them is still under study. Tentatively, however, we can say that our tactic has not given enough radiation to tumor cells. The dose to neoplasm at the surface of cut free of brain has been steadily increased from 4,000 to 16,000 rads. Normal brain received about  $1/3$  that amount. Among the 12 patients irradiated between 4 and 10 months ago there is but one excellent result. That we did achieve some destruction of tumor is suggested by a comparison between the next two pairs of figures. The radio-arsenic scan of a patient with a glioblastoma just before operation and the typical residual tumor seen 43 days after a grossly total removal via lobectomy, are seen in Fig. 5. In Fig. 6 are shown the scans of another patient just before operation and 56 days after similar surgery plus reactor radiation 34 days previously. Although almost no tumor can be seen here, it did recur and has since killed the patient.



Fig 3 General view of the right frontal lobe prepared for radiation. A white circular boron loaded ceramic cone surrounds the area of exposed brain. The anterior frontal zone of previous tumor removal is filled with an air inflated balloon (at 8 to 10 o'clock near periphery of inner circle enclosed by cone). This facilitates access of the slow neutrons to the cerebral area containing tumor remnants. Another lithium filled rubber balloon — 11 to 1 o'clock at periphery of inner circle — protects underlying temporal muscle from neutron radiation. The black flaps hanging down from the outer circumference of the white cone are a boron loaded plastic to protect the remainder of the head and neck from this radiation.

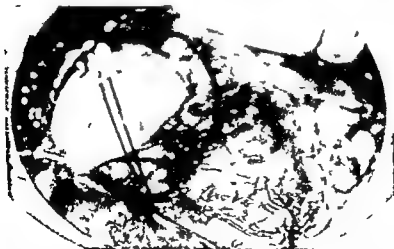


Fig 4 Close up view of site prepared for radiation. The air filled balloon in the area of previous frontal lobectomy is anchored in place by a silk suture through the dura reflected medially at the superior midline.

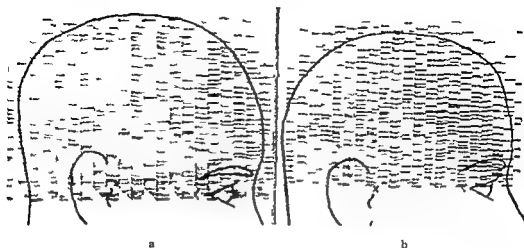


Fig 5 Posttrocephalograms in one and same patient a) Pre-operatively of a radioarsenic scan showing dense concentration in a posterior inferior frontal glioblastoma b) 43 days after grossly total removal of the glioblastoma. Abnormal isotopic uptake in the original area is still recognizable

In our next series which has already started with one patient we are giving sodium perhydrodecaborate  $\text{Na}_2\text{B}_{10}\text{H}_{12}$ . Advantages over our previous compound are (1) this molecule has a far greater percentage of boron (2) it is less toxic and we have given it in doses up to 50 mg of boron per kg of body

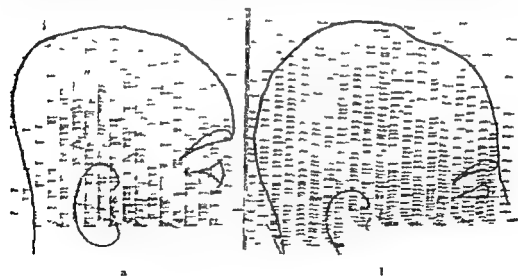


Fig 6 Posttrocephalograms in one and same patient a) Pre-operatively of a radioarsenic scan showing dense concentration in a temporo-parietal glioblastoma b) 34 days after grossly total removal of tumor and 34 days after boron slow neutron reactor therapy. More striking reduction in abnormal isotopic uptake than in the non irradiated patient in fig 5

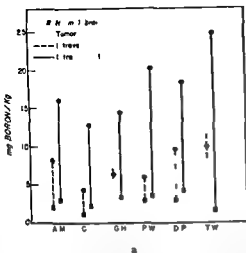
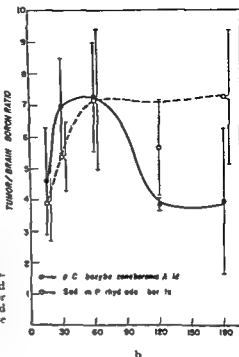


Fig 7 a) Glioblastoma multiforme sodium perhydro-decaborate Comparison between intravenous and intra arterial injections of uptake in brain and tumor in human subjects b) Mice studies with standard deviations Uptake of two boron compounds by mouse brain and mouse gliomas



weight without ill effect (3) it maintains a high tumor to brain ratio of nearly 7 to 1 in mouse gliomas longer than the paracarbox compound (Fig 7a) and (4) it is water soluble at pH 7.4 and can be injected directly into the common carotid artery distal to temporary occlusion of that vessel and with the external carotid tied off (Fig 7b). In the 6 patients illustrated here a portion of tumor and contiguous normal brain was removed following intravenous injection of 3 mg per kg of  $\text{Na B}_{10}\text{H}_{12}$ . Then about 1 hour later the same amount was injected directly into the proximally occluded ipsilateral common carotid artery and the extirpation of the tumor was concluded. We find an average of about 2 1/2 times as much boron in tumor after the second injection contrasting with 1 1/2 times as much in normal brain thereafter. We have exploited this tactic still further by irradiating our first patient after an injection of  $\text{Na B}_{10}\text{H}_{12}$  while both common carotid arteries were occluded. Another favorable change in our physical facility has occurred namely a doubled output of the reactor from 1 to 2 megawatts permitting a lowering of the unwanted gamma dose from the reactor core.

Aided by these two major changes we hope our next series of patients will show more satisfactory responses than the first group.

## Acknowledgements

We are grateful to the supporters of this research: U. S. Atomic Energy Commission under contract No. AT (30-1)-1093; National Cancer Institute; U. S. Public Health Service Grant No. C-3174; and a grant by the John A. Hartford Foundation on Isotopic Radiation Therapy of Neoplasms.

## SUMMARY

The most favorable among 140 boron compounds studied in mice bearing gliomas have been checked for their toxicity in larger animals and of these the six best have been finally assayed in man for use in neutron capture therapy by analyses of tissue uptake during craniotomy and by toxicity and excretion studies in terminal glioma patients. An initial series of 16 patients were irradiated using intravenous injection of paracarboxybenzene boronic acid made with boron 10. Dosimetric and operative techniques are described. Treatment of a second series has begun using an even less toxic compound containing far more boron and suitable for intracarotid injection following temporary occlusion of both the common carotid arteries.

## ZUSAMMENFASSUNG

Die aussichtsreichsten der 140 Bor-Verbindungen, die an Mäusen mit Glioma studiert wurden, wurden an grosseren Tieren bzgl. ihrer toxischen Wirkung untersucht. Die 6 besten Verbindungen wurden schliesslich am Menschen zwecks Neutronenbestrahlung ausprobiert, wobei die Aufnahme ins Gewebe während einer Kraniotomie, die Toxizität und die Ausscheidungsverhältnisse bei Patienten mit terminalen Gliomen studiert wurden. Zu Beginn wurde eine Gruppe von 16 Patienten unter Anwendung von paracarboxybenzen-Borsäure aus Bor 10 hergestellt, behandelt. Die dosimetrische und operative Technik wird beschrieben. Es wurde eine Behandlungsserie begonnen, wobei eine weniger toxische Verbindung zur Anwendung kam. Sie enthält bedeutend mehr Bor und eignet sich für Injektion in die Arteria carotis im Anschluss an temporären Verschluss beider AA. carotis commun.

## RÉSUMÉ

Parmi 140 composés du bore expérimentés sur des souris porteuses de gliomes, les plus favorables ont été testés au point de vue de leur toxicité sur des animaux plus gros. Les six meilleurs de ces composés ont été essayés sur l'homme en vue de leur utilisation pour un traitement par capture de neutrons; cette expérimentation faite sur des malades atteints de gliomes au stade terminal a comporté des analyses de fixation tissulaire au cours de craniotomies et des études de toxicité et d'excrétion. Une première série de 16 malades a été irradiée après injection intraveineuse d'acide paracarboxybenzène borique fait avec du bore 10. Les auteurs décrivent la technique du traitement et de la dosimétrie. Le traitement d'une seconde série a été entrepris avec un composé encore moins toxique contenant beaucoup plus de bore et utilisable en injection intracarotidienne après occlusion temporaire des deux carotides primitives.

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## NACHWEIS VON CEREBRALEN STRAHLENSCHADEN MIT RADIOAKTIVEN SUBSTANZEN

VON

SIGURD WENDE

Um den Einfluss einer Röntgen Tiefentherapie auf die Blut Hirn Schranke festzustellen, erfolgte bei Patienten, die wegen eines bösartigen Hirntumors bestrahlt wurden zu wiederholten Malen eine Gamma Encephalographie. Die technische Durchführung dieser Gamma Encephalographie wurde bereits in , Ergebnisse der Hirntumor Diagnostik mit radioaktiven Substanzen geschildert.

Wir führten weiterhin tierexperimentelle Untersuchungen durch um das erste Auftreten einer bestrahlungs bedingten Permeabilitäts Störung der Blut Hirn Schranke erfassen zu können.

Die Abb. 1 zeigt die Differenz Prozent Kurven einer Patientin mit einem Astrocytom rechts fronto parietal. Die beiden oberen Kurven geben die 2 Std. Werte vor und nach Beginn der Röntgen Therapie und gleichzeitiger RISA Injektion an. Es ist dabei deutlich zu erkennen, dass nach der 1. Röntgen Bestrahlung von 150 r auf die rechte Parietal Region eine erhebliche Impuls Zunahme gegenüber der 1. Messung bei der Voruntersuchung zu verzeichnen ist. 24 Std. später wurde die linke Parietal Region ebenfalls mit 150 r bestrahlt. Die anschließende Gamma Encephalographie zeigte ein unregelmässiges Kurvenbild. Zwar besteht noch immer ein Impuls Überwiegen der Tumor Seite, also auf der rechten Hemisphäre, über dem Bestrahlungsfeld. Bei Pr<sub>2</sub> ist es nun jedoch zu einer deutlichen Impuls Erhöhung gekommen.

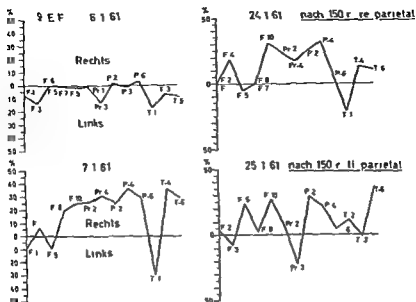


Abb 1 Differenz Prozent Kurven eines Astrocytoms vor und bei Röntgen Therapie

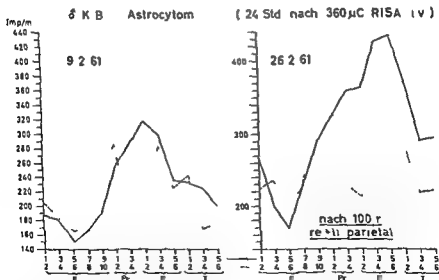


Abb 2 Impuls-Kurven eines Astrocytoms vor und bei Röntgen Therapie

Ein ähnliches Ergebnis zeigt die Abb 2. Es handelt sich dabei um einen Kranken mit einem Astrocytom links parietal. Auf der linken Seite des Bildes finden sich die Impuls Kurven 24 Std nach RISA Injektion. Die Impuls Erhöhung über dem Tumor Gebiet ist deutlich erkennbar. Die Kurven auf

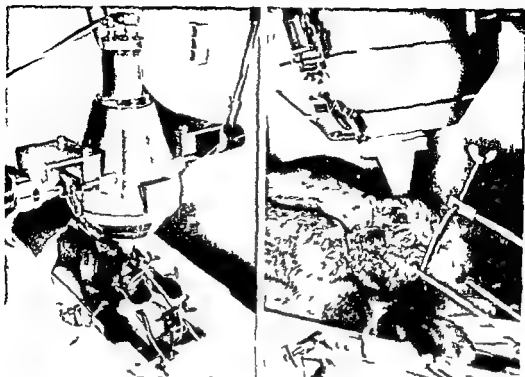


Abb 3 und 4 Tier Versuchsanordnung für die Isotopen Diagnostik

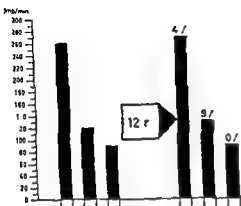
der rechten Seite des Bildes geben wiederum die Impuls Werte 24 Std nach RISA Injektion wieder. Diesmal erfolgte aber vorher eine Röntgen Bestrahlung des Gehirns mit 100 r rechts und links parietal. Durch diese Röntgen Therapie hat die Impuls Höhe über allen Hirnabschnitten deutlich zugenommen.

Die signifikante Impuls Erhöhung sofort nach Beginn der Bestrahlung lässt sich auf eine Permeabilitäts Störung der Blut Hirn Schranke zurückführen. Diese Permeabilitäts Störung macht sich im klinischen Bild mit einer Zunahme des Hirndrucks bemerkbar. Es tritt eine deutliche psychische Verlangsamung bis zur Somnolenz ein. Derartige Veränderungen können als Zeichen eines zunehmenden Hirnodems aufgefasst werden, das sich durch die Gamma Encephalographie objektivieren lässt.

Um Beginn und Ablauf des cerebralen Strahlenschadens bzw. des Hirnodems erfassen zu können, erfolgten tierexperimentelle Untersuchungen nach umschriebener Röntgen Bestrahlung des Gehirns.

Die Impuls Messungen über der Schadelkalotte wurden in gleicher technischer Anordnung durchgeführt, wie sie bereits bei der Patienten Untersuchung geschildert wurde. Als Versuchstiere wurden ausgewachsene Kaninchen

## Versuchsserie 12 r



## Versuchsserie 400 r

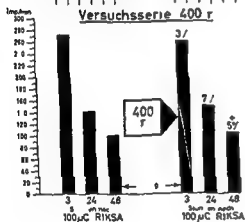
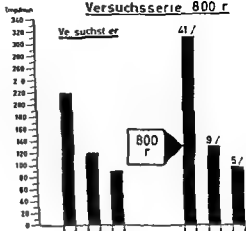


Abb 5 Impuls-Werte vor und nach Bestrahlung von 12 r bzw. 400 r

## Versuchsserie 800 r



## Kontrollser

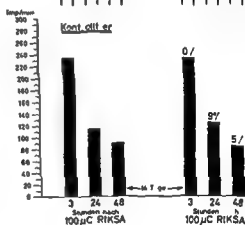


Abb 6 Impuls-Werte vor und nach Bestrahlung von 800 r

mit einem Durchschnittsgewicht von 2,5–3 kg verwandt. Die Tiere erhielten vor jeder Untersuchung zur Blockierung der Schilddrüse eine intravenöse Jod-Injektion; dann wurden 100  $\mu$ C radioaktiv jodiertes Kaninchen Serum Albumin (RIKSA) injiziert. Die Impuls-Messungen erfolgten 3 Std, 24 Std und 48 Std später. Bei der Untersuchung waren die Kaninchen auf einem Tierbrett fixiert; dadurch wurden Bewegungen des Kopfes mit den daraus resultierenden Messungenauigkeiten unmöglich. Die Messungen erfolgten bei freigelegter Schädelskalotte sowohl über der Area agranularis praecentralis als auch über der Area striata (Abb 3 und 4).

Nach einer Voruntersuchung zur Bestimmung des Ausgangswertes fanden dann im Abstand von 14 Tagen die weiteren Untersuchungen statt. Vor der 2. Isotopen-Injektion erhielten die Tiere eine einmalige umschriebene Röntgen-

## Versuchsserie 1500 r

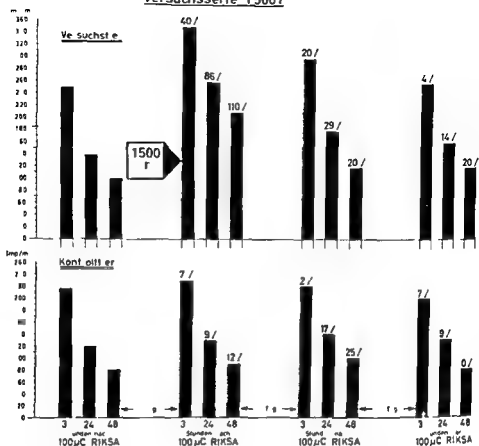


Abb 7 Impuls-Werte vor und nach Bestrahlung von 1500 r

gen Bestrahlung des Gehirns. Die verabfolgte Dosis betrug je Versuchstier 12 r — 5000 r. Jeweils 5 Tiere wurden zu einer Versuchsserie zusammengefasst, 3 Tiere wurden bestrahlt, 2 Tiere dienten zur Kontrolle. Der Abstand von 14 Tagen zwischen den einzelnen Untersuchungen wurde eingehalten, um eine vollständige Ausscheidung der vorher injizierten radioaktiven Substanz zu gewährleisten.

Die Abb. 5 zeigt die Impuls-Werte bei den Versuchsserien, 12 r und 400 r. Es ist zu erkennen, dass bei der Messung nach der Bestrahlung keine Erhöhung der Impulse gegenüber den Werten der Voruntersuchung aufgetreten ist. Die Versuchsserien, 25 r, 50 r, 100 r und 200 r zeigten das gleiche Ergebnis.

In der folgenden Abb. 6 sind die Werte der Versuchsserie, 800 r, wieder gegeben. Auf dem oberen Teil der Abbildung sind die Ergebnisse der Voruntersuchung und die Impuls-Höhen nach der Röntgen-Bestrahlung dargestellt.

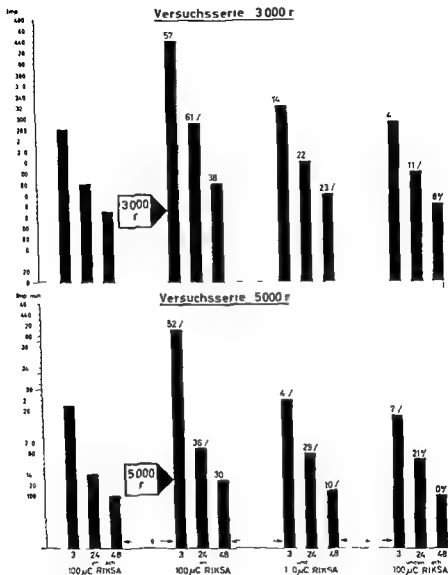


Abb 8 Impuls Werte vor und nach Bestrahlung von 3000 bzw. 5000 r

Es findet sich hier ein deutlicher Impuls Anstieg 3 Std. nach der Bestrahlung während die Werte 24 Std. und 48 Std. später keine Abweichung gegenüber der Voruntersuchung aufweisen. Der untere Teil der Abbildung zeigt die gleichbleibenden Mess Ergebnisse der Kontrolliere.

Noch deutlicher kommen die Veränderungen bei der Versuchsserie „1500 r“ zum Ausdruck. Wiederum auf der oberen Hälfte der Abb. 7 sind die Impuls

Hohen bei den bestrahlten Tieren angegeben Hier liegt der 3 Std Wert 40 % über dem Mess Ergebnis der Voruntersuchung Die Messungen nach 24 Std bzw nach 48 Std zeigen dass die Zunahme der Impulse pro Minute gegenüber der betreffenden Voruntersuchung sogar 86 % bzw 110 % beträgt Im Gegensatz zur Versuchsserie „800 r“ ist hier also nicht nur eine Impuls Erhöhung sondern auch ein erheblich verzögerter Abfall der Messwerte fest zustellen Die Untersuchung weitere 14 Tage später ergibt, dass die Impulse gegenüber den Ausgangswerten noch massig erhöht sind

Vergleicht man dazu die Messungen bei den Kontrolltieren der gleichen Serie (untere Hälfte des Bildes) so ist keine sichere Differenz zwischen den einzelnen Untersuchungen erkennbar

Die Abb 8 zeigt die Versuchsserien „3 000 r“ und „5 000 r“ Auch hierbei lässt sich wieder die erhebliche Zunahme der Impuls Höhe nach der Röntgen Bestrahlung erkennen

Aus den tiereperimentellen Untersuchungen kann geschlossen werden, dass nach einer umschriebenen Röntgen Bestrahlung des Gehirns eine Permeabilitäts Störung der Blut Hirn Schranke auftritt Sie stellt sich in ähnlicher Form auch nach der Röntgen Bestrahlung von Patienten mit Hirn Tumoren ein Diese Permeabilitäts Störung kann mit der Gamma Encephalographie durch die Zunahme der Impulse gegenüber dem Messergebnis der Voruntersuchung objektiviert werden Sie beginnt sofort nach der Bestrahlung und klingt dann allmählich ab Vier Wochen später ist die Ausgangslage wieder erreicht

Unsere Messergebnisse haben ihre Parallele in den histologischen Untersuchungen, bei denen sofort nach der Röntgen Bestrahlung des Gehirns ein perivaskuläres Ödem festgestellt werden kann das sich nach einiger Zeit wieder zurückbildet

## ZUSAMMENFASSUNG

Nach einer umschriebenen Röntgenbestrahlung des Gehirns stellt sich eine Permeabilitäts Störung der Blut Hirn Schranke ein die sich mit der Gamma Encephalographie objektivieren lässt

## SUMMARY

Localized roentgen irradiation of the brain causes increased permeability of the blood brain barrier which is demonstrable by means of gamma encephalography

## RÉSUMÉ

L irradiation roentgen localisée du cerveau augmente la perméabilité de la barrière hémocérébrale que l'on peut mettre en évidence grâce à la gamma-encéphalographie

## LITERATUR

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## FURTHER ATTEMPTS TO INFLUENCE THE ELIMINATION OF RADIOSTRONTIUM

by

ARNE NELSON, CURT ROSSBACK and LEVA ROSEN

In an earlier investigation the effect of Sr chloride, Sr lactate, Ca chloride, Ca lactate, Na lactate,  $\text{CaNa}_2\text{EDTA}$  and  $\text{CaNa}_2$  citrate on the elimination of radiostrontium after intraperitoneal injection was examined in mice (CARLQVIST & NELSON 1960). Only strontium salts and calcium sodium citrate of the tested agents were able to decrease the retention if given within half an hour before or after the administration of radiostrontium. The optimum effect was obtained with Sr chloride, the effect of Sr lactate being less. All other agents tested increased the retention.

In spite of the high number of animals giving statistically significant results we considered that some of them required further confirmation. It was therefore decided to repeat some of the investigations using a different method of measurement of the retention of radiostrontium. In the previous study  $^{90}\text{Sr}$  was used and the radioactivity was measured with a G.M. detector and a conventional scaler after ashing of carcasses (method I). In the present investigation  $^{89}\text{Sr}$  which is a  $\gamma$  emitter was employed and the retention in each animal measured after different intervals by means of a small animal counter with a plastic scintillator (method II).

From the Medical Division, Research Institute of National Defence, Department 1, Sundbyberg, Sweden. Submitted for publication 19 November 1962.



**Table 1**  
*Experimental conditions*

Agents	Concentration	Dose mM/kg	No of animals
Phys saline (controls)	0.9 %	—	30
Sr chloride	0.2 M	2.0	30
Sr lactate	0.2 M	1.5	30
Sr »	0.2 M	2.0	29
Ca chloride	0.2 M	1.0	53
Ca lactate	0.2 M	1.0	30
Ca «	0.2 M	1.5	28
Na »	0.2 M	1.0	29
Na »	0.2 M	2.0	28
Na rhodizonate	saturated	about 0.3	30
Mg sulfate	0.2 M	3.0	30
CaNa EDTA	0.2 M	2.0	30
CaNa EDTA	0.4 M	4.0	30
CaNa DTPA	0.2 M	2.0	60
CaNa DTPA	0.5 M	5.0	20

### Materials and Methods

*Mice* CBA mice males all aged 75 to 80 days, were used in the study, total number of animals 460 divided into groups of 8 to 10 as seen in Table 5

*Radiostrontium* Carrier free strontium 85 in nitric acid was neutralized and diluted with physiologic saline. Each animal was given a volume of 0.5 ml containing about  $0.1 \mu\text{C } ^{85}\text{Sr}$ . Due to the decay of the radionuclide the concentration of the radiostrontium solution had to be corrected in order to produce the same radioactive dose in the same amount of solution, i.e. 0.5 ml. The injections of radiostrontium were made intraperitoneally (i.p.)

*Agents* The different agents (see Table 1) were also administered i.p. to the animals 30 and 10 min before, and 10, 30 and 60 min and 24 hrs after the administration of radiostrontium. The controls received 0.5 ml normal saline at the time intervals given above. The doses of the various agents are expressed as millimoles per kilogram bodyweight (mM/kg).

*Measurements* The measurements have been performed with a 'small animal counter', built at our institute (Nelson 1961). The detector is a large well shaped plastic crystal the dimensions of the well are length 210 mm and diameter 90 mm. A photomultiplier tube with a relatively large cathode diameter, 110 mm, is attached to the scintillator. The effectiveness of the detector is about 30 %. A discrimination to give the best value of the ratio counts of sample/counts of background under the given circumstances was made (Rönnback 1962).

Table 2

*Retention in controls at different times after injection of  $^{85}\text{Sr}$  as percentage of initial measurement (percentage of dose administered)*

	Not corrected for decay	Corrected for decay
1 day	65.1	63.8
3 days	51.9	54.0
7 days	43.9	47.9
10 days	39.6	43.7
14 days	37.3	41.4
30 days	25.8	33.3
90 days	12.7	33.1

The animals contained in a cylindric plastic box with a diameter of 65 mm, were placed in the crystal in such a way that the centre of the animals lay on its central axis. The animals were measured within 3 min after injection and at 1, 3, 7 and 14 days after administration of  $^{85}\text{Sr}$  and were then sacrificed (except for the controls). The amount of  $^{85}\text{Sr}$  injected was calculated to give an initial count of  $63\,000 \pm 2\,000$  cpm.

### Results

The results of the measurements of the retention of  $^{85}\text{Sr}$  in the control group are seen in Table 2. The figures corrected for decay are also given. The results of the attempts to influence the retention of  $^{85}\text{Sr}$  by various agents are summarized in Table 3. The retention on the 7th day as percentages of the initial measurements, is given in Table 4. No correction has been made in this table for the decay of the nuclide during the fortnight since all the groups are treated in the same manner and the effect of decay is less than 9% after 7 days as shown in Table 2.

There was no statistically significant difference between the relatively small primary groups except in the case of strontium chloride. It was therefore considered justifiable to combine the groups in the following way: treatment 30 and 10 min before injection of  $^{85}\text{Sr}$  was designated pre-treatment; 10 and 30 min after injection early post-treatment; and at 1 and 24 hours late post-treatment.

The mean value of the retention of the control groups at 7 days has been used as the standard value with which the results for the treated groups have been compared. The results have been statistically treated (as indicated in Table 5). The  $t$  value and the significance level are calculated in order to compare the standard retention value of the controls and the retention of the treated group in question.

Strontium chloride decreased the retention of  $^{85}\text{Sr}$  if given as pre-treatment, early post-treatment or after 1 hour. Administration at 24 hours had no effect. The greatest and most unequivocal effect was obtained with early post-

Table 3

*Retention of  $^{85}\text{Sr}$  after treatment with various agents (percentage of dose administered)*

Agent	Dose mM/kg	Period of treatment	Days			
			1	3	7	14
Controls			65.1	51.9	43.9	37.3
Sr chloride	2.0	Pretreatment	51.7	37.0	32.0	25.3
		E. post treatment	51.6	34.8	28.7	23.3
		L. »	66.1	47.3	38.9	30.2
Sr lactate	1.5	Pretreatment	62.9	45.0	35.9	29.7
		E. post treatment	61.9	45.4	35.9	29.5
		L. »	65.5	50.9	40.3	33.2
Sr lactate	2.0	Pretreatment	51.4	36.2	29.5	23.9
		E. post treatment	66.2	48.5	38.9	31.0
		L. »	58.5	38.9	35.2	27.5
Ca chloride	1.0	Pretreatment	62.8	52.1	43.1	—
		E. post treatment	63.3	50.9	43.7	—
		L. »	64.3	52.0	43.9	—
Ca lactate	1.0	Pretreatment	82.4	66.0	52.2	39.6
		E. post treatment	79.1	61.8	49.4	40.7
		L. »	76.7	60.0	47.9	41.7
Ca lactate	1.5	Pretreatment	86.0	64.4	49.5	43.5
		E. post treatment	86.8	66.4	54.0	45.8
		L. »	80.7	63.7	56.8	47.6
Na lactate	1.0	Pretreatment	71.2	43.3	44.5	36.9
		E. post treatment	69.7	41.6	42.7	35.4
		L. »	66.7	39.0	42.0	35.0
Na lactate	2.0	Pretreatment	74.9	57.6	47.1	36.7
		E. post treatment	71.8	54.4	45.3	34.8
		L. »	71.3	56.6	47.7	36.5
Na rhodizonate	0.3 (about)	Pretreatment	68.1	—	47.2	39.4
		E. post treatment	68.5	—	45.9	40.3
		L. »	62.1	—	40.4	35.9
Mg sulfate	3.0	Pretreatment	50.3	35.5	30.4	28.0
		E. post treatment	51.9	37.1	32.7	28.9
		L. »	61.0	34.0	37.9	33.0
CaNa EDTA	2.0	Pretreatment	63.7	52.3	41.4	31.6
		E. post treatment	57.3	50.2	42.2	34.0
		L. »	64.6	52.9	43.7	36.3
CaNa EDTA	4.0	Pretreatment	63.2	48.9	41.3	33.3
		E. post treatment	63.5	48.3	41.5	33.3
		L. »	64.5	49.6	41.4	31.2
CaNa DTPA	2.0	Pretreatment	54.1	44.1	36.8	29.0
		E. post treatment	53.1	43.3	35.9	28.5
		L. »	59.6	47.6	37.8	30.3
CaNa DTPA	5.0	Pretreatment	57.6	47.6	37.8	28.8
		E. post treatment	57.2	41.6	36.0	27.8
		L. »	—	—	—	—

Table 4

*Retention 7 days after administration of  $^{85}\text{Sr}$  (percentages of dose administered)*

Agent	Dose mM/kg	Pretreatment		Early post treatment		Late post treatment	
		30 min	10 min	10 min	30 min	1 hour	24 hours
Phys saline (controls)	—	42.7 $\pm$ 0.7	40.3 $\pm$ 1.5	43.7 $\pm$ 0.8	41.2 $\pm$ 1.9	43.5 $\pm$ 1.6	44.2 $\pm$ 1.7
Sr chloride	2.0	32.0 $\pm$ 1.1	39.0 $\pm$ 1.2	29.1 $\pm$ 1.0	28.4 $\pm$ 0.4	35.5 $\pm$ 1.2	42.2 $\pm$ 1.6
Sr lactate	1.5	32.8 $\pm$ 0.9	39.0 $\pm$ 1.6	35.0 $\pm$ 0.9	36.8 $\pm$ 0.8	39.5 $\pm$ 0.0	41.1 $\pm$ 5.7
Sr lactate	2.0	29.6 $\pm$ 1.1	29.4 $\pm$ 1.7	38.2 $\pm$ 1.0	39.6 $\pm$ 1.5	34.6 $\pm$ 1.2	36.0 $\pm$ 1.6
Ca chloride	1.0	45.4 $\pm$ 1.9	40.7 $\pm$ 1.3	41.3 $\pm$ 1.5	46.1 $\pm$ 2.1	47.7 $\pm$ 2.8	40.1 $\pm$ 2.6
Ca lactate	1.0	57.6 $\pm$ 1.3	51.8 $\pm$ 1.1	49.3 $\pm$ 1.2	49.5 $\pm$ 1.2	49.9 $\pm$ 0.1	45.9 $\pm$ 1.6
Ca lactate	1.5	58.1 $\pm$ 4.1	44.3 $\pm$ 5.7	54.2 $\pm$ 2.3	53.7 $\pm$ 1.6	62.5 $\pm$ 4.0	51.1 $\pm$ 4.1
Na lactate	1.0	45.5 $\pm$ 1.7	43.5 $\pm$ 1.3	44.3 $\pm$ 1.7	40.6 $\pm$ 2.5	41.7 $\pm$ 1.7	47.3 $\pm$ 2.6
Na lactate	2.0	49.0 $\pm$ 1.0	45.6 $\pm$ 1.7	47.5 $\pm$ 1.7	42.6 $\pm$ 0.8	47.8 $\pm$ 1.9	47.6 $\pm$ 3.7
Na rhodizonate	0.3	46.7 $\pm$ 2.5	45.8 $\pm$ 1.3	48.9 $\pm$ 2.6	42.9 $\pm$ 1.1	40.8 $\pm$ 2.4	39.9 $\pm$ 1.9
	(about)						
Mg sulfate	3.0	32.1 $\pm$ 1.8	28.8 $\pm$ 1.6	33.2 $\pm$ 1.6	37.1 $\pm$ 1.4	35.3 $\pm$ 1.5	40.4 $\pm$ 1.1
CaNa EDTA	2.0	43.1 $\pm$ 1.0	39.7 $\pm$ 2.2	44.7 $\pm$ 3.0	39.6 $\pm$ 1.4	45.0 $\pm$ 1.4	42.3 $\pm$ 2.0
CaNa EDTA	4.0	44.3 $\pm$ 2.8	38.5 $\pm$ 3.5	41.6 $\pm$ 1.3	41.4 $\pm$ 1.4	42.1 $\pm$ 1.4	40.7 $\pm$ 2.7
CaNa DTPA	2.0	37.6 $\pm$ 1.5	35.9 $\pm$ 0.7	36.3 $\pm$ 0.7	35.4 $\pm$ 1.1	38.4 $\pm$ 1.6	37.2 $\pm$ 2.1
CaNa DTPA	5.0	37.9 $\pm$ 2.0	35.6 $\pm$ 1.4	34.8 $\pm$ 2.0	3.1 $\pm$ 0.8	—	—

treatment. As no significant difference between 0.5, 1 and 4 mM/kg was observed on the effect of retention, 2 mM/kg was used for the complete examination. The influence of strontium lactate was also statistically significant but inferior to that of strontium chloride. The effect of magnesium sulfate on the retention was of the same order of magnitude as that of strontium chloride. The concentration used was 3 mM/kg which appeared to be the optimal dose.

CaNa<sub>2</sub>DTPA was inferior to strontium chloride and magnesium sulfate in decreasing the retention but of the same order as strontium lactate. There was no significant difference between 2 and 5 mM/kg.

Calcium chloride had no effect and calcium lactate increased the retention. Sodium lactate had no statistically significant effect.

Independent of concentrations and times, CaNa<sub>2</sub>EDTA had no effect on the retention; neither had sodium rhodizonate.

### Discussion

The results of the present investigation (method II) as well as these results in the light of the previous study (method I) based on the difference between the treated groups and the control groups in the two studies as seen in Table 6, will be considered. If the retention value of a treated group is lower than that of the control group the deviation value has been given a negative sign.

The results from the control groups in method II show much smaller varia-

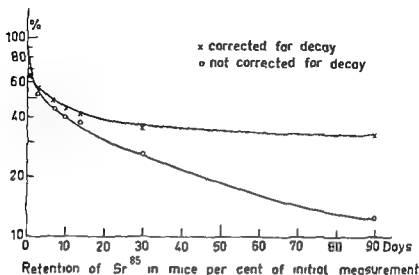


Diagram (see text on p. 137)

tions in spite of a lower number of animals in the groups, which indicates that method II as could be expected is more accurate.

The control animals in method I showed a significantly higher retention of radiostrontium (47.8 %) than those in method II (43.9 %). The fact that  $^{85}\text{Sr}$  was used in the first and  $^{90}\text{Sr}$  in the second case cannot explain the difference, since in both cases carrier free strontium was used. In the first case (CARLQVIST & NELSON 1960) special animals were used as blanks in order to obtain initial radiation values for calculating the retention in the control groups as well as in the treated groups.

Among previous attempts to influence the elimination of radiostrontium MACDOYALD (1955), CLARA (1960) and CATSCH & MELCHINGER (1959) succeeded in decreasing the skeletal retention of strontium 90 by the injection of inactive strontium salts in rats. An effect was evident in their investigations only if the stable strontium was given practically simultaneously with  $^{90}\text{Sr}$ . CATSCH & MELCHINGER tried increasing doses of stable strontium and found that the effect was not linear. A relative increase in the skeletal retention was observed with high doses.

No dose dependent effect of inactive strontium was observed within the dose range investigated in the present study.

The present retention values in mice are much lower than the retention of  $^{90}\text{Sr}$  in rats reported by CATSCH & MELCHINGER. These authors used, however, strontium 90 chloride and investigated only the retention in the femur.

Table 5  
Statistical treatment of results

Agent	Dose mM/kg	Period of treatment	No of mice	Retention mean $\pm$ SE	t values and significance levels
Controls	0.5		30	$43.9 \pm 0.6$	—
Sr chloride	2.0	Pretreatment	10	$37.0 \pm 0.8$	12.7
		E. post treatment	10	$28.7 \pm 0.5$	20.3
		1 hour after	5	$35.5 \pm 1.2$	66.27
		24 hours after	5	$42.2 \pm 1.6$	0.99
Sr lactate	1.5	Pretreatment	10	$35.9 \pm 1.4$	*5.44
		E. post treatment	10	$35.9 \pm 2.1$	3.704
		L. »	10	$40.3 \pm 1.5$	2.264
Sr lactate	2.0	Pretreatment	10	$29.5 \pm 0.9$	13.3
		E. post treatment	10	$38.9 \pm 0.9$	4.81
		L. »	9	$35.2 \pm 0.9$	*7.98
Ca chloride	1.0	Pretreatment	20	$43.0 \pm 1.2$	0.67
		E. post treatment	19	$43.6 \pm 1.4$	1.97
		L. »	15	$45.2 \pm 2.2$	0.57
Ca lactate	1.0	Pretreatment	10	$52.2 \pm 0.8$	8.47
		E. post treatment	10	$49.4 \pm 0.8$	5.79
		L. »	10	$47.9 \pm 1.5$	1.85
Ca lactate	1.5	Pretreatment	8	$49.5 \pm 4.4$	1.25
		E. post treatment	10	$54.0 \pm 1.3$	7.11
		L. »	10	$56.8 \pm 3.5$	3.675
Na lactate	1.0	Pretreatment	10	$44.5 \pm 1.0$	0.51
		E. post treatment	9	$42.7 \pm 1.5$	0.75
		L. »	10	$42.0 \pm 1.5$	1.172
Na lactate	2.0	Pretreatment	9	$47.1 \pm 1.1$	2.539
		E. post treatment	9	$45.3 \pm 1.3$	1.00
		L. »	10	$47.7 \pm 2.0$	1.87
Na rhodionate	0.3 (about)	Pretreatment	10	$46.2 \pm 1.3$	1.61
		E. post treatment	10	$45.9 \pm 1.7$	1.11
		L. »	9	$40.4 \pm 1.5$	2.16
Mg sulfate	3.0	Pretreatment	10	$30.4 \pm 1.3$	9.44
		E. post treatment	10	$32.7 \pm 1.0$	*9.57
		L. »	10	$37.9 \pm 1.2$	4.48
CaNa EDTA	2.0	Pretreatment	10	$41.4 \pm 1.3$	1.84
		E. post treatment	10	$42.2 \pm 1.8$	1.28
		L. »	10	$43.5 \pm 1.2$	0.15
CaNa EDTA	4.0	Pretreatment	10	$41.3 \pm 2.4$	1.07
		E. post treatment	10	$41.5 \pm 0.9$	*3.31
		L. »	10	$41.4 \pm 1.5$	1.59
CaNa DTPA	2.0	Pretreatment	20	$36.7 \pm 1.1$	5.76
		E. post treatment	20	$35.9 \pm 0.7$	8.70
		L. »	20	$37.8 \pm 1.3$	4.27
CaNa DTPA	5.0	Pretreatment	10	$36.8 \pm 1.2$	5.26
		E. post treatment	10	$36.0 \pm 1.1$	6.37
		L. »	—	—	—

—  $p \leq 0.05$  —  $p \leq 0.01$  —  $p \leq 0.001$

Table 6

Comparison betw. in the ashing method I ( $^{90}\text{Sr}$ ) and SAC method II ( $^{85}\text{Sr}$ ) percentage of dose administered

		Method I	Method II	t values
Controls		47.8 ± 0.9	43.9 ± 0.6	13.611
Difference between treated groups and control groups				
Agents	Dose mM/kg	Method I	Method II	t values
Sr chloride	2.0	-7.1 ± 1.66	-11.9 ± 1.00	2.474
		-10.9 ± 1.66	-13.2 ± 0.78	2.337
		-14 ± 1.76	-8.4 ± 1.34 <sup>a</sup>	3.153
			-1.7 ± 1.11 <sup>b</sup>	0.121
Sr lactat	1.5	-3.9 ± 1.58	-8.0 ± 1.5 <sup>c</sup>	1.864
		-5.1 ± 1.92	-8.0 ± 2.18	0.997
		3.1 ± 1.42	-3.6 ± 1.62	3.116
Sr lactate	2.0	-2.7 ± 2.10	-14.4 ± 1.08	4.923
		0.1 ± 2.99	-5.0 ± 1.08	2.016
		3.8 ± 1.50	-8.7 ± 1.03	6.757
Ca chloride	1.0	18.4 ± 2.38	-0.9 ± 1.34	7.070
		19.1 ± 2.29	-0.3 ± 1.5 <sup>c</sup>	7.055
		17.4 ± 2.01	1.3 ± 2.8	5.216
Ca lactate	1.0	13.1 ± 9.94	8.3 ± 1.00	1.548
		11.6 ± 2.29	5.5 ± 1.00	2.440
		9.9 ± 1.84	4.0 ± 1.6 <sup>c</sup>	2.418
Ca lactat	1.5	19.3 ± 2.58	8.6 ± 4.44	0.991
		15.0 ± 2.20	10.1 ± 1.43	1.810
		14.0 ± 1.58	12.9 ± 3.56	0.284
Na lactat	1.0	3.6 ± 1.84	0.6 ± 1.17	1.316
		6.2 ± 1.92	-1.2 ± 1.6 <sup>c</sup>	1.937
		3.6 ± 1.4 <sup>c</sup>	-1.9 ± 1.6 <sup>c</sup>	3.418
Na lacta	2.0	13.0 ± 2.38	1.2 ± 1.25	3.679
		8.1 ± 1.92	1.4 ± 1.43	2.797
		5.0 ± 1.58	3.8 ± 2.09	0.458
Ca/Na EDTA	2.0	-1.1 ± 2.29	-9.5 ± 1.43	0.519
		4.5 ± 1.58	-1.7 ± 1.90	2.510
		6.9 ± 1.6	-0.2 ± 1.31	12.896
Ca/Na EDTA	4.0	11.4 ± 2.75	-2.6 ± 2.48	13.184
		3.2 ± 1.84	-2.6 ± 1.08	1.793
		6.1 ± 1.50	-2.5 ± 1.62	3.89

a — treatment after 1 hour ■ — treatment after 24 hours —  $p \leq 0.05$  \* —  $p \leq 0.01$  —  $p \leq 0.001$

on the second day after administration. The retention in the present investigations was generally measured on the 7th day and on the whole animal. It may be seen from Table 2 and the diagram that the retention at day 1 and day 3 is 65 and 54 % respectively, which however is in better agreement with the results of CATSCH & MELCHINGER.

The inactive strontium salts were able to decrease the retention of radiostrontium as in the previous study. Strontium chloride was the most effective salt, the effect was still apparent when it was administered at one hour after  $^{85}\text{Sr}$  but not at 24 hours. The decreasing effect after one hour could not be shown in our previous study, probably due to the great variations between the groups.

Strontium lactate was not as effective as strontium chloride. This an ion effect appears especially with early post treatment. This effect was significant when calcium chloride and calcium lactate were compared.

The an ion effect observed with sodium lactate in the previous study appears this time only as a tendency.

The present studies in mice have confirmed the results of previous investigations in rats with regard to the effect of inactive strontium on the deposition of strontium 90.

The effect of non radioactive strontium salts is apparently a carrier effect, and as late post treatment has no effect, a release of radiostrontium already fixed in the skeleton cannot be expected.

The calcium salts had no decreasing effect on the retention of radiostrontium as in the previous study, calcium chloride which previously gave a great increase in retention, was this time without any effect.

The effects of calcium on the retention of radiostrontium (MACDONALD, SPENCER et coll 1956, CATSCH & MELCHINGER) appear to be inconsistent in agreement with earlier investigations. The possibility of a systematic error in the previous investigation with regard to the calcium chloride group can of course not be entirely excluded.

It was found that  $\text{Mg}^{++}$  caused a decreased retention of the same magnitude as strontium chloride in accord with MACDONALD, CATSCH & MELCHINGER and CLARKE et coll (1959).

COHN & GONG (1953) and VAUGHAN & TUTT (1953) tested mixed calcium and sodium salts of EDTA but reported no effect on the excretion of  $^{85}\text{Sr}$ , which result was confirmed in the present investigations.

Contrary to the excellent effects on the retention of plutonium with sodium DTPA, no effect was observed on radiostrontium by KRIEGER & MELCHINGER (1959) and CATSCH & MELCHINGER. A significant decrease of about 80 % of the controls was obtained in the present study. The sodium calcium salt of DTPA was used however in a concentration ten times higher than that employed by CATSCH & MELCHINGER without any apparent side effects.

No decreasing effect of sodium rhodizonate other than that to be expected



was observed, in accord with the results of other investigators (KRIEGLER & MELCHINGER and VOLF 1959) The Na and K salts of rhodizonic acid apparently have the ability of selectively binding strontium, even in the presence in great excess of calcium (LINDENBAUM et coll 1957, 1958)

### Acknowledgement

The authors wish to express their thanks to Miss Ingegerd Andersson for her technical assistance

### SUMMARY

The results of the application of a method in which strontium 85 was measured in living animals by means of gamma spectrometry were found to be in good agreement with those of previous attempts to influence the retention of radiostrontium in mice when strontium 90 was used. The effects of numerous agents on the retention are reported and discussed.

### ZUSAMMENFASSUNG

Die Resultate einer Methode womit Strontium 85 in lebenden Versuchstieren mit Hilfe von Gamma Spektroskopie gemessen wurde zeigten gute Übereinstimmung mit früheren Untersuchungen über die Beeinflussung der Retention des Strontium 90 bei Mäusen. Der Einfluss von verschiedenen Mitteln auf die Retention wird erörtert.

### RÉSUMÉ

L'application d'une méthode de mesure du radiostrontium 85 sur des animaux vivants par spectrométrie gamma a donné des résultats en bon accord avec ceux d'essais antérieurs pour influencer sur la rétention du radiostrontium sur des souris dans lesquels on avait utilisé le strontium 90. Les auteurs signalent les effets de nombreux facteurs sur cette rétention et les étudient.

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## COMPUTATION OF DOSES IN DERMATOLOGIC ROTATION THERAPY

by

P RYNNÉ

GREEN JENNINGS & HENDTLASS (1951) worked with a voltage of 50 kV at a focus skin distance of 50 cm to treat large areas of the human skin with a minimum of tube settings. WAGNER (1955) and SCHIRREN (1955) have given treatments at focus skin distances of 100 and 200 cm respectively. While at a distance of 100 cm it is necessary to use four radiation fields to cover the front as well as the back of a patient, SCHIRREN found it sufficient to use one field for each at a FSD of 200 cm. A drawback common to the procedures used by WAGNER and by SCHIRREN is that the sides of the patient are insufficiently irradiated due to the grazing incidence of the radiation.

The possibility of applying the techniques of rotation therapy in an attempt to achieve a more uniform distribution was considered. A revolving disk was installed in the floor of a treatment room and on this the patient could stand and support himself with his hands on a coupled bar mounted under the ceiling. The roentgen tube was fixed with the central ray directed horizontally and intersecting the vertical axis of the revolving disk. A Maclett OEG 60 tube was chosen for the treatments, this is provided with a 1 mm Be window at the end of the tube housing and is said to have a more homogeneous field than other tubes for superficial therapy. The tube was energized with a Dermopan apparatus and operated at 50 kV, 25 mA and a total filtration of 1 mm Be.

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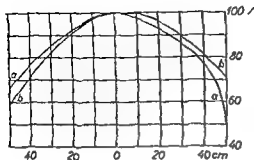


Fig 1 Field inhomogeneity in the 100 cm plane

The dose rate  $D$  in the central ray was first measured at a focus distance of 100 cm. The direction of the central ray was found visually as the line connecting a point source of light placed 100 cm from the focus and its image in a small mirror placed in contact with the Be window. The dose rate measurements were carried out with a Kustner Panzerdosimeter supplied with a Kurzkammer which was adjusted by reference to a parallel plate standard chamber using radiation of the same quality.

The percentage variation of the dose in a plane perpendicular to the central ray at 100 cm focus distance is shown in Fig 1. Curve  $a$  represents the relative dose distribution along a horizontal line while curve  $b$  is the dose distribution in the vertical direction. The tube was mounted with the water inlet directed downwards. It can be seen that the irradiation field was most homogeneous in the vertical direction. It is possible to draw isodose curves for the entire 100 cm plane with reasonable accuracy (Fig 2) from the curves  $a$  and  $b$  of Fig 1.

The absorption curves in skin equivalent material for radiation at 100 cm and respectively 200 cm focus distances are shown in Fig 3. In the former case the first HVL was found to be 1.35 mm tissue and the second HVL 1.85 mm tissue.

The following simplifications are made to facilitate a calculation of the dose for a full revolution of the patient.

- 1 The dose is calculated only for a horizontal section through the patient at the level of the central ray.

- 2 This section is approximated by an ellipse with the semi axes  $b = 12$  cm (from the axis of rotation to the skin surface over the sternum and spine respectively) and  $a = 19$  cm (from the axis of rotation to the sides of the thorax).

- 3 The axis of rotation is placed 115 cm from the focus coinciding with the centre of the ellipse. The FSD in the direction of the central ray will then vary from 103 cm (focus sternum and focus spine, respectively) to 96 cm (from focus to either side of thorax).

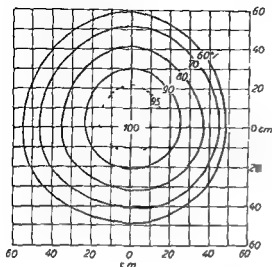


Fig 2 Isodose curves in the 100 cm plane

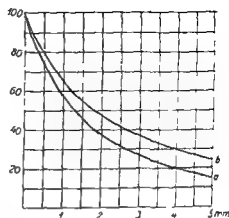


Fig 3 Curves of absorption in tissue equivalent material curve *a* at a focus distance of 100 cm curve *b* at a focus distance of 200 cm

In Fig 4  $SS_1$  represents the track followed by the xiphi sternum in a rotation of the patient by  $\alpha$  (degrees) from the central ray FO. The dose rate received to the sternum in the position  $S_1$  is given by

$$d_{\alpha} = k_1 k_2 k_3 D = k_{\alpha} D$$

where

$D$  is the dose rate at the point of reference C of the central ray  $FC = 100$  cm

$k_1$  is a correction taking account of the inhomogeneity of the field from C to  $S_1$

$k_2$  is a factor correcting for the decrease of the dose rate from  $S_2$  to  $S_1$  according to the inverse square law

$k_3$  is a correction factor for the decrease of the dose rate due to absorption in the air between  $S_2$  and  $S_1$

To find the correction factors for different values of  $\alpha$  it is necessary to calculate  $x$ ,  $y$  and  $r$  in Fig 4. This may be done with the aid of the simple trigonometric formulae

$$x = \frac{100}{115 - 12 \cos \alpha} - 12 \sin \alpha$$

$$y = \sqrt{115^2 + 12^2 - 2 \cdot 115 \cdot 12 \cos \alpha}$$

$$r = \sqrt{100^2 + x^2}$$

Since curve *a* (Fig 1) is not symmetrical with respect to the central ray an average value of  $k_1$  has been used in the table this means that the irradiation of the xiphi sternum is considered to be equal for positive and negative values of  $\alpha$

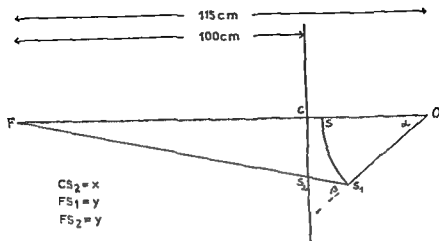
The values of  $x$ ,  $y$  and  $r$  have thus been calculated for  $\alpha = 0, 10, 20, 30, 40, 50, 60, 70, 80$  and by using these results one finds the values of

$k_1$  from curve *a* (Fig 1)

$$k_2 \text{ from } k_2 = \left(\frac{r}{y}\right)^2$$

$k_3$  from curve *a* (Fig 3)

considering that  $(y - y')$  cm air correspond to  $(y - y')/80$  mm tissue

Fig 4 Geometry of irradiation at sternum  $\alpha$  degrees from the central position

The dose for one revolution may be calculated with sufficient accuracy if the time  $T$  for one turn is divided into 36 sections of equal size for which the dose to the sternum is given by

$$T/36 \frac{d_a + d_a + 10}{2}$$

The total dose in one revolution will, therefore be  $D_a = \frac{T}{36} 2 (0.5 d_a + d_{10} + d_{20} +$

$$+ 0.7 d_{30}) = \frac{T D}{18} (0.5 k_a + k_{10} + k_{20} + + 0.7 k_{30})$$

where  $\equiv g$   $k_{10} = k_1$   $k_2$   $k_3$  for  $\alpha = 10$  degrees At an angle of  $\alpha = 84^\circ$  the radiation will strike the sternum tangentially The correction factors  $k_1$   $k_2$  and  $k_3$  as well as their product  $k_a$  are given in the table for different values of  $\alpha$

If a calculation of the dose at 1 mm depth is also desired  $d_a$  must be corrected by a further factor  $k_4$  to take care of absorption in a skin layer of thickness  $z$  which the radiation has to penetrate If the surface of the skin is considered to be a plane within a small area around the upper sternum we have  $z = 1/\cos \beta$  where  $\beta$  is the angle of incidence (Fig 4) which can be computed from the relation

$$\sin \beta = \frac{115}{y} \sin \alpha$$

Table

Calculations of dose on sternum focus-axis of rotation 115 cm

	$k$	$k$	$k$	$\equiv$	$k =$ $k_1 k_2 k_3$	$k_a =$ $k_1 k_2 k_3 k_4$
0	1.00	0.94	0.98	0.58	0.92	0.54
10	1.00	0.94	0.98	0.57	0.92	0.53
20	0.99	0.93	0.98	0.56	0.90	0.51
30	0.99	0.91	0.97	0.53	0.88	0.47
40	0.98	0.89	0.95	0.49	0.83	0.43
50	0.98	0.87	0.94	0.42	0.80	0.33
60	0.97	0.84	0.93	0.32	0.76	0.24
70	0.97	0.81	0.91	0.20	0.72	0.14
80	0.97	0.78	0.90	0.00	0.69	0.00

For the calculated values of  $z$  the factor  $k_a$  can be read from the absorption curve  $a$  in Fig. 3. The total correction factor  $k_a = k_1 k_2 k_3 k_4$  is then calculated for all values of  $a$  and the dose  $D_1$  at 1 mm depth may be evaluated by analogy with  $D_0$ .

Similar calculations have been carried out for the sides of thorax, the only difference being that  $b$  ( $\approx 12$  cm) is replaced by  $n$  ( $\approx 19$  cm). An attempt has here been made however to estimate the influence of the curvature of thorax on the thickness of the absorbing layer. The difference between the  $z$  values found by the two methods is considerable only for larger values of  $a$  and  $\beta$ . A value of  $z = 44$  mm was for example, found by the primitive method, as compared to  $z = 11$  mm with the more exact calculation for  $a = 80$ . Both of these thicknesses will however only permit a small percentage of the radiation to penetrate to a depth of 1 mm. It was consequently found that the depth dose calculated by taking the curvature of the surface into account exceeded the former value by only 2 %.

The dose at other points of the elliptical cross section must lie between those at the sternum and at the sides of the thorax. These differ by only 10 %. Nevertheless a computation was also carried out for a point P of the ellipse the radius vector of which subtends an angle of  $45^\circ$  with the principal axes. From the formula of ellipse expressed in polar coordinates

$$\rho^2 = \frac{b^2}{1 - e^2 \cos^2 \nu}$$

the distance  $\rho$  from P to the axis of rotation is found to be 14.4 cm since  $\nu = 45^\circ$  and

$e = \sqrt{\frac{a^2 - b^2}{a^2}} = 0.775$ . The surface dose may then be calculated with the formulae given above.

The angle of incidence is found to be  $23.2^\circ$  degrees when point P of the ellipse is located on the central ray. By turning the ellipse in one direction from the central ray ( $\alpha$  negative) the angle of incidence will become  $\gamma = \beta + 23.2^\circ$  degrees while for a turn in the opposite direction ( $\alpha$  positive)  $\gamma = \beta - 23.2^\circ$  degrees. The irradiation will consequently not be symmetrical with respect to the central ray and it will be necessary to calculate the depth dose for each interval of  $10^\circ$  degrees ranging from  $\alpha = -60^\circ$  to  $\alpha = +107^\circ$ .

We then arrive at the following results

$D = 150$  r/min at 100 cm focus distance

*Surface dose per revolution*

Sternum and spine  $D = 0.375$   $D \cdot T = 56.3$  T roentgen

Sides of thorax  $D_0 = 0.415$   $D \cdot T = 62.2$  T »

Point of  $45^\circ$  ( $D_a = 0.383$   $D \cdot T = 57.5$  T » )

Mean value  $D = 0.393$   $D \cdot T = 59.2$  T roentgen

*Dose in 1 mm depth per revolution*

Sternum and spine  $D_1 = 0.163$   $D \cdot T = 24.5$  T roentgen

Sides of thorax  $D_1 = 0.182$   $D \cdot T = 27.3$  T »

Point of  $45^\circ$  ( $D_1 = 0.165$   $D \cdot T = 24.8$  T » )

Mean value  $D_1 = 0.172$   $D \cdot T = 25.9$  T roentgen

T min is the time for a full revolution

Similar measurements and calculations have been carried out with a distance of 215 cm between the focus and the axis of rotation. The curves showing the inhomogeneity of the field in the 200 cm plane are found to have almost the same shape as curves *a* and *b* of Fig. 1, with the exception that the figures on the abscissa should be doubled. From the absorption curve *b* of Fig. 3 the first HVL is found to be 1.85 mm tissue and the second HVL 3.0 mm tissue. It will be noted that the radiation is considerably more penetrating than in the 100 cm plane.

$D = 20$  r/min at 200 cm focus distance

*Surface dose per revolution*

Sternum and spine  $D_s = 0.410$   $D/T = 11.2$  T roentgen

Sides of thorax  $D_s = 0.433$   $D/T = 8.7$  T »

Mean value  $D_s = 0.421$   $D/T = 8.4$  T roentgen

*Dose in 1 mm depth per revolution*

Sternum and spine  $D_1 = 0.215$   $D/T = 4.3$  T roentgen

Sides of thorax  $D_1 = 0.229$   $D/T = 4.6$  T »

Mean value  $D_1 = 0.222$   $D/T = 4.4$  T roentgen

The dose received by skin areas lying above or below the central section will be smaller than the calculated values. This is due to the inhomogeneity of the field in the vertical direction and — in the case of the depth dose — to the more oblique incidence as well. A calculation of these doses will, however, become considerably more complicated because of the three dimensional geometry and also due to the fact that an approximation by an ellipse will be rather rough. To find an upper limit of the dose per revolution it will generally be sufficient to use those values that can be found by multiplying the previously calculated values for the central section,  $D_s$  and  $D_1$  with a correction factor  $k_v$ , which accounts for the inhomogeneity of field in a vertical direction. This factor may be read from curve *b* in Fig. 1.

### Acknowledgement

The help received from Dr H. Kopp of the Dermatologic Department is gratefully acknowledged.

### SUMMARY

A method of covering large areas of the skin by rotating the patient during the treatment is described. The dose per revolution of the patient is calculated for the surface of the skin and for 1 mm depth at distances of 115 cm and 215 cm respectively between the focus and the axis of rotation.



## ZUSAMMENFASSUNG

Eine Methode die zur umfangreichen Bestrahlung grosser Hautflächen mit Hilfe von Rotation der Patienten führt wird beschrieben. Die Strahlendose an der Oberfläche und in 1 mm Tiefe wird für je eine Umdrehung des Patienten für einen Abstand Fokus Rotationsachse von 115 cm bezweck 215 cm angegeben.

## RÉSUMÉ

L'auteur décrit une méthode d'irradiation de grandes surfaces de peau par rotation du malade au cours du traitement. La dose par révolution du malade est calculée pour la surface de la peau et pour une profondeur de 1 mm à des distances foyer axe de rotation de 115 cm et 215 cm.

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## RELATION BETWEEN FIELD SIZE AND TOLERANCE OF RABBIT'S BRAIN TO ROENTGEN IRRADIATION (200 kV) VIA A SLIT-SHAPED FIELD

by

NILS O BERG and MARTIN LINDGREN

It has long been known that the tolerance to roentgen radiation varies with the area and volume of tissue irradiated MOPPET (1931) who used rats appears to have been the first to show that the skin erythema dose increases rapidly with decreasing size of small fields (below 10 mm in diameter) As far as the skin is concerned, the relationship between the erythema dose and tolerance dose respectively, and the area of the field irradiated have been studied by many workers in this field (JOLLES 1939 1941 1953, ELLIS 1942 MacKEE, MUTSCHELLER & CIPOLLARO 1943, GOLDBERG 1944 JOLLES & MITCHELL 1947 and JOYET & HOHL 1955) Various theories and formulae have been suggested to explain this co-variation

The relation between the volume of the irradiated tissue and the tolerance dose of inner organs has however received less attention More precise knowledge of this relation for small areas of the CNS has become urgent since the introduction of stereotaxic radiosurgery of the brain (LEKSELL 1951 1957) Ultrahard radiation provides the best possibilities of analysis in this respect (TOBIAS 1952 LIDEN 1957, LARSSON LEKSELL REXED & SOURANDER 1959) Using conventional radiation BERG & LINDGREN (1958) made a comprehensive

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Table 1

*Survey of treatment scheme and data of survival in the different groups*

Width of slit in mm	Skin dose in r	Fields	Animals	Animals irradiated over 2 fields	Number of animals with neurosymptoms	Survival in weeks Range	Mean	Deaths from intercurrent disease
1	18 000	5	5	0	0	—	52	0
2	27 000	6	11	11	11	1—2 1/2	18	0
	18 000	5	5	0	2	—	52	1
	13 500	5	5	0	0	—	52	0
	9 000	11	8	8	0*	14—52	42.7	2
	3 000	12	11	9	0	—	52	0
4	9 000	5	5	5	5	37—52	46.8	0
	5 000	5	5	0	1	—	52	0
	3 000	6	6	6	0*	22—52	47	1
6	5 000	5	5	3	4	32—52	48	0
	3 000	5	5	0	0*	26—52	43.8	2
8	3 000	8	8	4	1	18—52	43.5	2
12	3 000	5	5	0	3	32—52	48	0
	2 100	5	5	0	0	—	52	0
30*	3 000	20	20	0	18	25—52	44.3	0
	2 500	10	10	0	6	46—52	51.1	1*
	2 100	10	10	0	2	39—52	50.5	0
	1 700	6	6	0	0	—	52	0

\* Groups from a previous investigation inserted for comparison

analysis of the late cerebral lesions in rabbit following irradiation of half of the brain. The relatively small focus of the apparatus (4 mm) enabled extension of the investigation to include even narrow fields.

The present investigation is concerned with the morphology and frequency of delayed radiation lesions in the rabbit's brain following different roentgen doses delivered via a slit varying in width from 12 mm to 1 mm.

### Material and Methods

Eighty-two rabbits weighing 2 to 3 kg and received in litters of 2 to 10 animals were distributed as equally as possible among the different groups to be irradiated. The animals were irradiated under deep urethane anesthesia. Table 1 gives slit width, skin dose and number of animals treated in the different

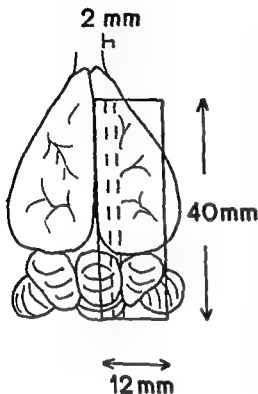


Diagram 1 Position of the 2 mm and the 12 mm slits over the rabbit's brain

Diagram 1 Lead shielding — 2 mm thick — prevented irradiation of the rest of the animal

The animals were under careful observation and they were weighed regularly. After 52 weeks all the surviving animals were bled under anesthesia. The brain was fixed in formalin and sectioned systematically in the way described by BERG & LINDGREN (1958). The lesions were noted on standard diagrams (Diagrams 3 to 9) showing the extent of cerebral lesions in representative vertical sections through the brain. The animals were killed 52 weeks after irradiation if survival time is not given in the legend. The dots indicate vascular lesion and glial cell in otherwise normal tissue; the hatched areas denote subtotal destruction of cerebral tissue; and black areas denote cysts or frank necrosis.

*Technical data* Roentgen machine Muller MG 300 kV 200 half value layer 0.93 mm Cu, focus skin distance 250 mm dose rate about 100 r per min, dose control by a Philips dosimeter.

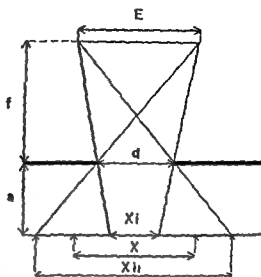
The depth dose of the central beam at different widths of the slit was cal-

culated. The experiment was carried out in two series, irradiated at an interval of about one year. Some of the animals in the first series died within 3 months from gangrene of one of the legs after injection of urethane in 25 % solution into the thigh. These animals were excluded and the brain was not examined histologically. In the other series 12.5 % urethane was injected subcutaneously without subsequent complications. Each group treated consisted of at least 5 animals.

During irradiation the head was carefully fixed in position by 4 clamps placed in a frame with the head gripped infraorbitally and occipitally. The slits were 40 mm long and 12, 8, 6, 4, 2 and 1 mm wide, respectively. The central beam was directed towards the middle of the slit. The medial border of the slit was placed about 3 mm lateral to the midline of the skull. The position of the slits over the rabbit's brain is illustrated in

Diagram 2 Geometry of the beam to illustrate calculation of penumbra and effective width of the field  $x$  at different depths  $a$

- $r$  diameter of focus  
 $d$  slit width  
 $f$  focus skin distance  
 $x$  central beam  
 $x$  central beam + total penumbra



culated according to ALSOPP (Central Axis Depth Dose Data, Brit J Radiol Suppl 5, 1953) without correction for elongation of the field. The unscreened beam and breadth of penumbra at different depths was calculated according to Diagram 2 modified according to LIDÉN (1957). It is clear from the figure that

$$\lambda_i = d - \frac{a}{f}(E - d) \quad (1)$$

$$\lambda_u = d + \frac{a}{f}(E + d) \quad (2)$$

The contribution by the penumbra was therefore

$$\lambda_u - \lambda_i = 2 \frac{aE}{f}$$

The penumbra at depth,  $a$ , did not vary with the width of the slit,  $d$ .

According to equation (1),  $\lambda_i \approx 0$ , and  $d = 1$  mm gives  $\lambda_u = 83.3$  mm. This means that a central homogenous field was irradiated through the entire brain even when the narrowest slit was used. The position of the lesions in the brain tissue showed that the most deep seated lesions in the brain (21 mm) and in the medulla (34 mm) had been irradiated with a homogenous beam. The relation between the homogenous beam and the surrounding penumbra was least favourable for the 1 mm field. For the most deep seated brain regions irradiated with this width of slit the homogenous beam was 0.70 mm wide and the width of the penumbra was 0.34 mm on either side. This relation was much more favourable for the other lesions observed on irradiation via wider slits (see Table 2).

Table 2

*Distribution of different types of lesions and data for most deep seated lesions in the animals*

Width of slit in mm	Skin dose in r	No of fields	Fields with out lesions	Discrete lesions	Severe lesions	Depth # in mm of most deep seated lesion L	Effective width Y of field in L in mm	Depth dose in L in r
1	18 000	5	0	4	1	21	$1.04 \pm 0.34$	10 800
2	27 000	5	0	0	6	—		
	18 000	5	0	1	4	—		
	13 500	5	0	5	0	(19)		8 600
	9 000	11	0	2	0	10	$2.08 \pm 0.16$	7 100
	3 000	12	12	0	0	—		
4	9 000	5	0	3	2	(30)		4 300
	5 000	5	1	4	0	19	$4.30 \pm 0.30$	3 200
	3 000	6	0	0	0	—		
6	5 000	5	0	1	4	(28)		2 500
	3 000	5	3	1	1	18.5	$6.43 \pm 0.29$	2 000
8	3 000	8	3	1	4	20	$8.64 \pm 0.32$	1 950
12	3 000	5	1	0	4	(28)	$12.31 \pm 0.50$	1 850
	2 100	5	4	1	0	21	$13.35 \pm 0.45$	1 700
30	3 000	20	2	2	16	34	$38.45 \pm 0.53$	1 500
	2 500	10	0	0	10	23		1 700
	2 100	10	2	6	2	13	$33.3 \pm 0.21$	1 750

The exact distribution of the intensity in the penumbra is not known. The effective width,  $Y$  of the field was defined as the homogeneously irradiated zone + half the penumbra with an accuracy of  $\pm$  half the penumbra  $/\pm \frac{1}{2}(Y - \lambda)$ . This value for  $Y$  is surely somewhat too high. Calculation for a 2.0 mm slit thus showed a homogeneously irradiated central field 1.92 mm in width at a depth of 10 mm and the effective width is given as  $2.08 \pm 0.16$  mm.

### Results

Those animals that received 27 000 r via a 2 mm slit deteriorated rapidly they became soporose and all died within 18 days. Marked gross cerebral edema with depression of the cerebellum in the foramen magnum was noted as well as a strip showing hyperemia and petechial hemorrhages. Microscopic examination showed recent necroses with petechial hemorrhages in the irradiated tissue as well as marked edema of the adjacent tissue. The changes involved both the grey and the white matter. This group was not analysed further.

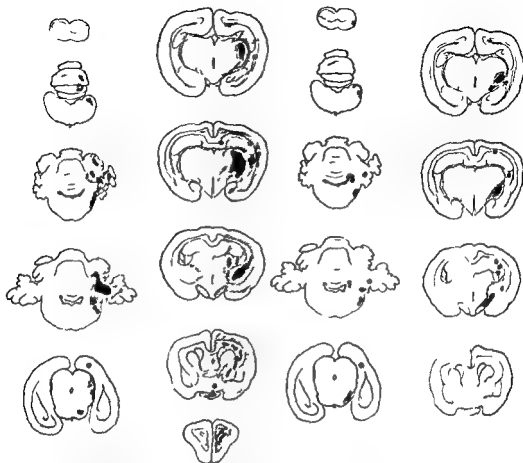


Diagram 3 Dose 3 000 r/12 mm Large necrotic areas mainly in white substance extension of lesion as after irradiation through a 30 mm slit in previous investigation

Diagram 4 Dose 5 000 r/6 mm Mainly well demarcated necrosis in white substance at a depth of about 20 mm This animal died 32 weeks after irradiation

(For explanation of symbols see text p. 149)

In the other groups only few of the animals died. The frequency of neurologic signs is given in Table 1. The dominating symptom was 'turning of the head to the treated side' (12 animals). A few animals 'walked in circles' and had nystagmus and convulsions. These symptoms and signs were often followed by emaciation. In some animals (1 animal — 18 000 r/2 mm slit, 3 animals — 5 000 r/6 mm slit, 1 animal — 3 000 r/12 mm slit) the loss of body weight might have been due to paralysis of the masticatory muscles, with consequent oblique abrasion of the edge of the teeth and chewing difficulties. These animals probably had an injury of nervus trigeminus in the base of the skull.

The microscopic picture of the lesions one year after irradiation via narrow fields of varying width was largely the same as that described in detail on p.

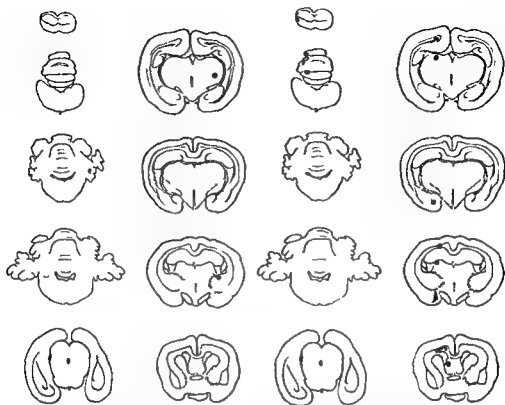


Diagram 5 Dose 5000 r/4 mm Minimal vascular lesions at a depth of 15 mm

Diagram 6 Dose 9000 r/4 mm slit to left and 2 mm slit to right Several small lesions in different parts of brain after irradiation via 4 mm slit

(For explanation of symbols, see text p 149)

radiation of half the brain (slit width 30 mm) in a previous investigation (BERG & LINDGREN 1958 pp 47—62) That investigation included fractionated and single dose irradiation, but only the effects of single doses are referred to here Three types of histologic lesions were recognized namely discrete changes partial destruction and necrosis The occurrence of these changes in the present material is first illustrated

*Discrete changes* in otherwise undamaged brain tissue These consisted of old and recent petechial hemorrhages (Fig 1) endothelial swelling fibrinoid necrosis (Fig 2) or hyalinization of the vessel walls teleangiectasis (Fig 3) and small perivascular glial scars (Fig 4)

*Partial destruction* included partial degeneration of the myelin (Fig 5) or partial loss of nerve cells (Fig 6) and fibrinoid imbibition



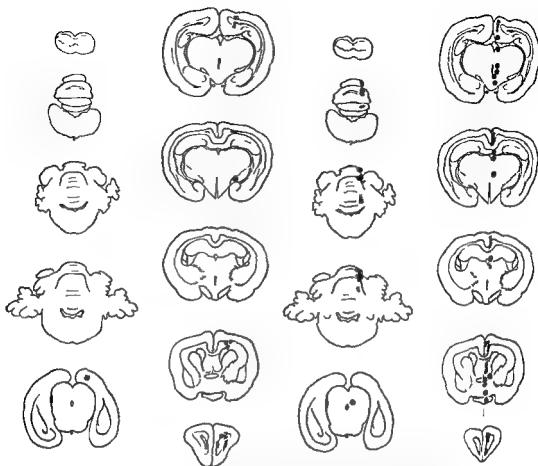


Diagram 7 Dose 13 500 r/2 mm. Mainly small vascular lesions in white matter; no necrosis.

Diagram 8 Dose 18 000 r/2 mm. Postnecrotic scars and vascular lesions; distortion of field in section through optic chiasm.

(For explanation of symbols see text p. 149.)

**Necrotic changes.** Frank necrosis occurred with or without cysts and completely gliovascular destruction of tissue, often with proliferation of atypical glial cells (Figs 7 and 8).

The lesions in those rabbits that were irradiated through a 1 mm and 2 mm slit deserve further illustration. In these brains the necrosis did not undergo gross cystic degeneration, not even after a dose of 18 000 r. After one year the destroyed tissue was, as a rule, absorbed and the defect was compressed by the surrounding tissue. The final defects were often surprisingly small (Fig. 9).

The radiation lesions were readily recognized in the white substance in preparations stained for myelin (Figs 10 and 11). Gliovascular changes were

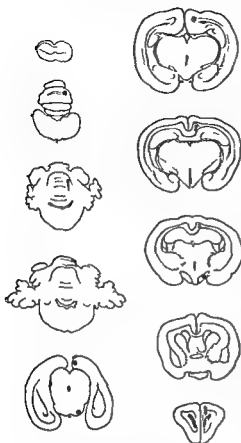


Diagram 9 18 000 r/2 mm Discrete lesions mainly in white substance (See diagram 7 for comparison)

(For explanation of symbols see text p 149)

often very slight, particularly areas close to the slit, the beam was best defined. Cerebral edema and vascular lesions were sometimes seen in deeper parts of the irradiated area however. The lesions closely resemble those by a 185 MeV proton beam with width (REXED MAIR, E. LARSSON and LEKSELL 1966).

Delivery of large doses through narrow slits often damages meningeal vessels nearest the radiation. Splitting, fatty degeneration and thickening of the vessel walls, reduction of the lumina and damage to the surrounding meninges were observed (Figs 12 and 13).

On gradation of the lesions according to the above mentioned degrees of severity it was difficult to distinguish between partial and severe injury. Lesions more than 4 mm in width (Fig. 11) were therefore taken as a single group (severe lesions). In the previous investigations, the lesions were almost always of capillary origin. In the cerebral tissue they were confined to the capillary bed.

distribution of the injuries among the different groups of animals (Table 2)

Typical examples of the distribution of the injuries in the brain are shown in Diagrams 3 to 9. In all these diagrams the radiation lesions were localized to the irradiated field. Severe as well as discrete lesions were seen in grey substance (cerebral and cerebellar cortex, central nuclei, substantia nigra, optic chiasm), white substance (oval center, cerebellar medulla, optic chiasm) (Figs 3, 4, 6 and 8). A high frequency of lesions in the white substance had been noted in a previous investigation where a slit width of 1 mm had been used. It is evident from Diagrams 5, 7 and 9 that even narrow slits (1 to 4 mm) damaged the white substance more extensively after irradiation with marginal doses.

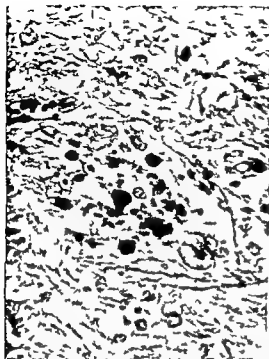


Fig 1 Small capillary hemorrhage with proliferation of glial cells and iron deposits in white substance 13 500 r/2 mm Hematoxylin & eosin  $\times 700$



Fig 2 Thickening and fibrinoid degeneration of vascular wall in optic chiasm 18 000 r/2 mm Hematoxylin & eosin  $\times 210$

A skin dose of 13 500 r/2 mm (Diagram 7) is a relatively small dose. When this dose was exceeded (Diagram 8) widespread lesions in both white and grey substance occurred in most animals (Table 2).

The rabbits irradiated through a 30 mm slit often showed large hemorrhages but those irradiated through the narrow slits did not (Table 3). On the other

Table 3

*Frequency of large hemorrhages and tumors in the irradiated animals*

Width of slit in mm	Group	Skin dose in r		Hemorrhages (large)		Tumours
				Frequency	Number fatal	
1 and 2	2	13 500	18 000	0/15	—	—
	4	5 000	9 000	0/10	—	—
	8	3 000	5 000	2/10	—	1 malignant glioma
	11	3 000		1/8	—	—
12		2 100	3 000	1/10	—	—
30		2 100	2 500	11/40	4	1 osteogenic sarcoma
		3 000				

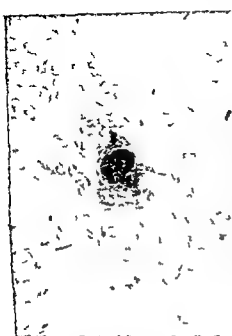


Fig 3 Recent hemorrhage in telangiectatic vessel in oval center (depth from skin about 7 mm) 18 000 r/1 mm Hematoxylin & eosin  $\times 11$



Fig 4 Glial scar with proliferation of glial cells and endothelial cells 13 500 r/2 mm Hematoxylin & eosin  $\times 480$

hand petechial hemorrhages in cerebral tissue were common in all groups (Figs 1, 3 and 14). One animal that had received 3 000 r/6 mm slit showed an undifferentiated glioma close to an area of complete gliovascular destruction (Fig 15). No osteogenic sarcomas were seen.

### Discussion

*Correlation between width of slit, radiation dose and irradiation injury.* In an attempt to elucidate these relations the changes noted were analysed in two ways: (1) determination of the frequency of injuries in each group as judged by a standardized examination method and (2) determination of the lowest focal doses delivered via slits of varying width that produced morphological changes.

1. Diagram 10 gives the distribution of the lesions according to severity in the different groups. In this log-log diagram the doses given refer to skin doses, and the width of the slit to the width of the beam at the surface of the skin. It is obvious that the injurious effect of irradiation decreased markedly with the width of the slit and that the frequency of the lesions decreased with every



Fig 5 Partial destruction of myelin sheaths in white substance of oval center 18 000 r/1 mm Spilmeyer  $\times 43$

Fig 6 Upper region: Vacuoles and glial cell proliferation in white substance. Lower region: Partial loss of nerve cells in the hippocampus 18 000 r/2 mm Hematoxylin & eosin  $\times 83$



Fig 6

decrease of the dose. The only exception was that seen in those groups in which half the brain was irradiated (width of slit = 30 mm) i.e. the group from a previous investigation (BERG & LINDGREN 1958, and unpublished experiments) included in Table 1 for comparison.

A tolerance index was calculated from Diagram 10. Each discrete lesion was given 1 point, and each severe lesion 3 points. The absolute score noted in each group was then converted into percentage of maximum attainable. By graphical interpolation and extrapolation the dose expected to give a score of 50 % was calculated for each width of slit. For each dose delivered the width of the slit expected to give a score of 50 % was calculated in the same way.

This procedure is largely the same as giving the width of the slit and the dose, respectively, that produced necrosis in 50 % of the animals. Discrete lesions were included in the score in order to obtain a more reliable index for the groups consisting of only a few animals.

The 50 % scores noted are given in Diagram 11 where they are joined to a curve (curve A). The curve rises markedly with decreasing width of slit, and the curve is S shaped, i.e. the ascent appears to decrease when the slits are very narrow.

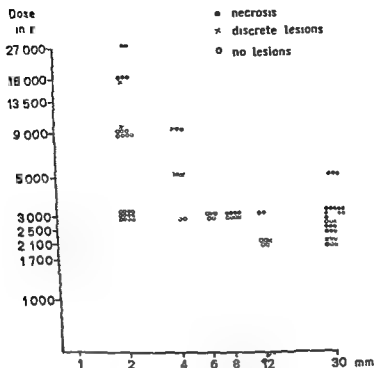


Diagram 10 Results of the morphologic analysis of the rad at on lesions in rabbit's brain in relation to skin dose and width of field plotted in a log log diagram

2 The second procedure, which was used to analyse the relation between irradiation injury and width of the beam, is illustrated in Table 2 which gives the focal doses for those lesions situated farthest from the source of radiation in every group and the effective width of the field at the levels of the lesion

These doses are plotted in the log log diagram (Diagram 11) and the curve (B) thus shows the variation of the tolerance dose with width of slit. The maximal width of the field, corresponding to the limit for the entire penumbra, is also given in the diagram. Curve B is also S-shaped and a good agreement between the two curves is obvious.

This agreement does not exclude a number of sources of error influencing the slope and the shape of the curves. The skin doses appear to be fairly accurate. For the calculated depth doses (curve B) the error may be about 5%. The increasingly poorer definition of the width of the tissue irradiated with increasing depth is another source of error which is important when narrow fields are used. Only 5 animals were irradiated via a slit of 1 mm width. The

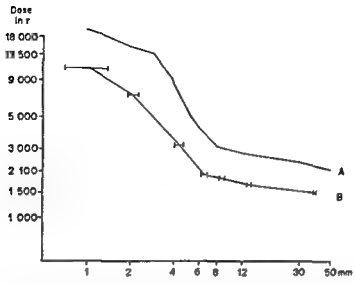


Diagram 11 Correlation between width of field radiation dose and radiation injury in rabbit's brain. Curve A: Tolerance index based on frequency of lesions after irradiation with a given dose (skin) through a given width of slit. Curve B: Lowest focal dose giving morphologic lesions in relation to effective width of field for different groups of animals.

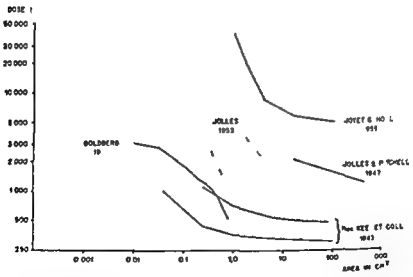


Diagram 12 Area factor for skin tolerance according to literature. JOYET and HOLL used fractionation of dose (18 sessions in 22 days). The other curves are based on a single irradiation.

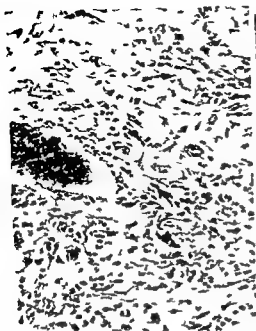


Fig 1



Fig 2



Fig 9

Fig 7 Complete destruction of tissue with proliferation of atypical glial cells 3 000 r/2 mm Hematoxylin & eosin  $\times 180$

Fig 8 Cortical scar with vacuoles and moderate gliosis 18 000 r/2 mm Hematoxylin & eosin  $\times 83$

Fig 9 The central edematous zone with microcytosis represents the compressed irradiated field 30 000 r/2 mm Hematoxylin & eosin  $\times 43$





Fig 10 Vertical sections through rabbit brain in myelin impregnation. The extension of the scar (arrow) is clearly seen on comparison of the two halves of the brain (see also fig 11) 18 000 r/2 mm width.  $\times 8$

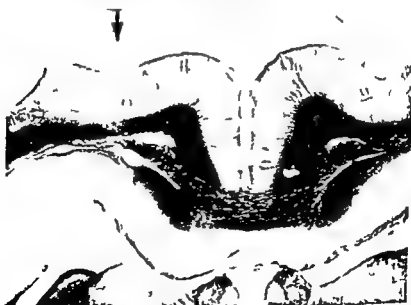


Fig 11 Preparation as in fig 10 from another rabbit. The scar is situated further from midline. a cortical scar is seen (arrow). the cystic spaces are not true cysts but dilations of the lateral ventricle on the base of contraction of the scar. 18 000 r/2 mm width.  $\times 8$



Fig 12 Onion like fibrosis and thickening of the wall of an arachnoid vessel 18 000 r/2 mm width v Giesson stain

focal dose found surely exceeds the tolerance dose because all the animals showed injuries. The lowest focal dose for this width was not stated.

The use of wider slits is accompanied by a different source of error. With slits more than 8 mm wide part of the lateral border of the slit lies outside the brain and then adjacent tissue is included in the irradiated field. The brain is broadest about 34 mm (in cerebellum) so that when a 30 mm slit is used over half of the brain, only about 17 mm brain tissue is irradiated but at the same time heterogeneous tissues of bone, ears, cartilage, muscles and skin are included. It is not known to what extent irradiation of these tissues might influence the results. It is, however, obvious that the lower limbs of the curves are relatively well defined whether the effective width of the slit is 17 mm or 30 mm (Diagram 11).

Even the use of a rectangular field instead of an ideal circular field may impair the accuracy of the dose levels of the curves (JOLLES and MITCHELL 1947). Despite these sources of error the following conclusions appear to be warranted.

The two curves are based on different types of morphological changes. Curve A shows largely the frequency of necrosis in the cerebral tissue and curve B the frequency of discrete small lesions of vascular type. Most of the changes are confined to the capillaries. The fact that the curves are of the same shape may support the assumption that also necrosis develop from primarily vascular injuries. This is supported still further by morphological observations of SCHOLZ 1934, RUSSEL, WILSON & TANSLEY 1949, BERG & LINDGREN 1958.



Fig 13 Fat metamorphosis in vascular wall of arachnoidal vessel. Slight cellular proliferation and abundant fine fat droplets. Scarlet R stain. 480



Fig 14 Marked destruction of tissue and vascular changes along the wall of the third ventricle in the center of the field. partial or complete destruction. 18 000 r/2 mm. H. mastocytin & eosin. 43

and others. Large doses, however, cause complete destruction of the tissue. Such destruction has been observed and interpreted as a primary injury of the nervous tissue (ARNOLD, BAILEY & LAUGHLIN 1954, SCHUMMELEDER, F. SCHNER, BERGNER & KROGH 1961). Since the capillaries appear to be the most radiosensitive structures in the brain and since extensive diffuse capillary injury to the CNS invariably results in necrosis, their experiments do not warrant any definitive conclusions concerning the sensitivity of the nervous structures.

A recent publication by LARSSON (1960) on the blood-brain barrier in early stages of necrosis following irradiation with 185 MeV proton beam of 3 mm diameter are of interest. 10 000 rad produced no necrosis within an observation period of max. 162 days, while 20 000 rad produced necrosis in all the animals that survived 11 to 14 days. His analysis suggests that the injury to the capillaries occurs before and is probably the direct cause of severe damage to the parenchyma.

EMAN, CURTIS, GEBHARD & HAYMAKER (1959) using deuteron beams noted that the dose required to produce histologic lesions in mouse brain was between

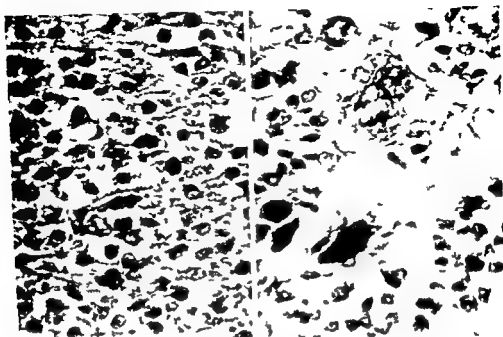


Fig. 15 Different parts of an undifferentiated glioma with occasional giant cells. 3 000  $\times$  6 mm. The tumour was situated close to an area of radiation necrosis with marked proliferation of atypical glial cells (see fig. 7 from same animal). Haematoxylin & eosin  $\times$  710.

15 000 rad and 30 000 rad with a beam 1 mm in diameter. With microbeams 25  $\mu$  in diameter the threshold dose was approximately  $10^4$  rad. They concluded that microbeams cause a predominantly direct radiation injury to the brain substance because vessels were only occasionally located within the beam path. Furthermore the lesions were sharply delimited and did not follow any vascular distribution pattern. Their results are based on observations 24 days after exposure and delayed vascular lesions after exposure to doses below the threshold doses cannot be excluded.

*Analysis of shape of curves.* The relation found between the tolerance dose and field size was not reliable enough to serve as a basis for mathematical analysis but the shape of the curve can be discussed in more general terms. Ionizing radiation initially produces both reversible and irreversible changes. The recovery of reversible changes is a process presumably dependent on various accelerating and inhibitory factors. LAMARQUE 1942, JOLLES 1950, TOBIAS et coll 1952, JOYET & HOHL 1955 and BACQ & ALEXANDER 1955 have discussed the importance of the formation of toxic substances following irradiation. If these

substances are diffusible into adjacent non irradiated tissues, the shape of the tolerance curve will vary considerably with the volume of tissue into which such substances can diffuse JOYET & HONIL used a diffusion model and found good agreement between the expected and observed values for variation of the skin tolerance with the volume of tissue irradiated within field sizes of 1 to 100 cm<sup>2</sup>. The steep rise of our curves found on reduction of the width of the slit from 12 to 4 mm is also compatible with the existence of a diffusion process. Diffusion processes may thus influence recovery after irradiation but the experiments teach nothing of the direction of any such diffusion.

DEVIL (1957) has clearly shown that recovery of irradiated epithelial cells in the skin of mice is dependent upon substances diffusing from non irradiated to irradiated cells and such substances may be assumed to be active also in brain tissues.

According to the diffusion theory the tolerance dose for irradiation of very small fields should be extremely high. But as is apparent from the curves this is not so. With a field width of 2 mm the curve showed an initial tendency to flatten. This may be explained in different ways. Thus, on irradiation with these large doses the irradiation time was so long (max. 3 hours) that it could disturb the course of the curve: the biological substrate may change and/or the permeability to diffusible substances may increase. The fact that protective substances from surrounding tissues may be available only to a certain extent, might also be of significance.

We feel, however, that some other factor is of decisive importance. The recovery phenomenon can reconstitute only part of the initial changes following irradiation. Sooner or later a dose may be achieved where the irreversible part of the radiation changes dictates the shape of the curve. The results of ZEMAN et coll. (1959) indicate, however, that the inverse relationship between radiosensitivity and tissue volume exposed holds for microbeams (25  $\mu$  diameter).

*Area factor for skin and brain.* The skin seems to be the only tissue studied in details for the area factor (JOLLES & MITCHELL 1947, LILLIS 1942, JOULEY 1953, GOLDBERG 1944, MACHLEE et coll. 1943, JOYET & HONIL 1955 and others). There is general agreement that the tolerance varies inversely with the size of the field. A graphical demonstration of a number of observations reported in the original papers is given in Diagram 12 in log-log scale. This diagram covers fields of varying shape and size from 150 cm<sup>2</sup> down to 0.01 cm<sup>2</sup>. None of the investigations include a study of such variation in field size as to produce an S-shaped curve. If values forming the basis of the curves given by GOLDBERG and by MACHLEE et coll. are combined, however, they would give an S-shaped curve for the skin.

In the present investigation an S-shaped curve was found for the brain. With a modification of the experimental conditions it might be possible to demonstrate an S-shaped curve also for the skin in one and the same experiment.

## SUMMARY

The relation between field size and tolerance of rabbit's brain to roentgen irradiation via slit shaped field 12 mm to 1 mm wide has been studied. Single skin doses between 2 100 r and 27 000 r were given. After 52 weeks the morphology of the lesions was analysed. The frequency of injuries as well as the lowest focal dose which produced lesions were determined. The effect of irradiation decreased markedly with reduced width of slit. The resulting curves for the occurrence of necrosis and for discrete lesions are both S shaped. The shape of the curves is discussed especially the influence of diffusion processes. Published data on the area factor makes it likely that the tolerance curve for the skin will be S-shaped too.

## ZUSAMMENFASSUNG

Der Zusammenhang zwischen der Feldgrösse und der Toleranz des Kaninchengehirns gegenüber Röntgenbestrahlung mit Feldern von 12 mm bis 1 mm Spaltbreite ist studiert worden. Einzelbestrahlungen mit Hautdosen zwischen 2 100 r und 27 000 r wurden gegeben. Die Morphologie der strahlenbedingten Hirnveränderungen wurde 52 Wochen nach der Bestrahlung analysiert. Die Frequenz der Schäden sowie die niedrigste Herddosis welche einen Schaden hervorrief wurden bestimmt. Die Wirkung der Bestrahlung nahm deutlich mit Verminderung der Spaltbreite ab. Die sich ergebenden Kurven für das Auftreten von Nekrosen sowie von diskreten Veränderungen sind S förmig. Die Form der Kurven wird diskutiert insbesondere der Einfluss von Diffusionsprozessen. Bereits veröffentlichte Oberflächenfaktoren machen es wahrscheinlich dass die Toleranzkurve auch für die Haut einen S förmigen Verlauf hat.

## RÉSUMÉ

Les auteurs ont étudié l'influence des dimensions du champ sur la tolérance du cerveau de lapins à l'irradiation roentgen par un champ en forme de fente de 12 mm sur 1 mm de large. Ils ont donné des doses uniques de 2 100 r à 27 000 r. Ils ont étudié la morphologie des lésions au bout de 52 semaines. Ils ont déterminé la fréquence des lésions ainsi que la plus petite dose focale ayant causé des lésions. L'effet de l'irradiation décroît beaucoup quand on réduit la largeur de la fente. Les courbes d'apparition de la nécrose et de lésions discrètes ont toutes deux une forme en S. Les auteurs étudient la forme de ces courbes et en particulier l'influence des processus de diffusion. Il est vraisemblable d'après les données publiées sur le facteur surface que la courbe de tolérance de la peau a aussi une forme en S.

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## COBALT, COPPER AND IRON IN ANEMIA ASSOCIATED WITH RADIOTHERAPY OF TUMORS

Preliminary communication

by

ERNO AUTIO and JOUKO SAIKKONEN

One of the main problems in the treatment of malignant diseases by radiotherapy is the protection of healthy tissue from the injurious effects produced by irradiation. The hematopoietic system is particularly sensitive to ionizing radiation (WARREN & BOWEN 1950) and its reactions must be continuously followed. Leukocytes, especially lymphocytes, are the cells most affected, although the erythroblasts are almost equally susceptible (BLOOM & BLOOM 1947) and anemia resistant to any kind of treatment may develop. Moreover, since anemia is often associated with many forms of malignant tumors, the management of such cases during radiation therapy may be difficult.

Cobalt has been used in various anemias resistant to iron, vitamins and liver extract. These conditions were briefly summarized by ROTHLEY *et coll.* (1956) who stated that cobalt medication is indicated in anemia due to infection, rheumatoid arthritis, myxedema, nephrosis, tumors and leukemia as well as in hemolytic anemia. They furthermore recommended the use of cobalt simultaneously with copper and iron. These three metals are all included in the compound CCF 37 (Sandoz AG, Basel) which is supplied in the form of tablets containing 5 mg cobalt, 11.5 mg copper and 22 mg iron. These tablets



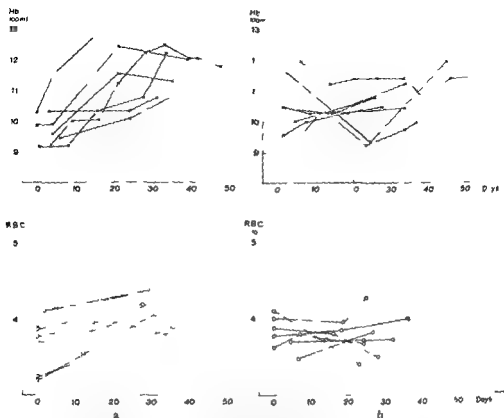


Fig. 1. Diagrams showing the erythrocyte counts and hemoglobin values respectively in 7 patients with carcinoma of the breast treated a) with CCF 37 tablets, b) with Ferronitum.

have been tested by NORDENSON (1961), who obtained good results in certain chronic anemias resistant to iron.

The erythropoietic effect of cobalt in many animal experiments has been shown to be remarkable. Anemia produced by a diet low in protein (ORTEN & ORTEN 1945) and anemia following hypophysectomy (CRAFTS 1952) may be reversed to polycythemia by cobalt. SAIKKONEN & MARTTINEN (1963) demonstrated that erythropoiesis in rats may be reactivated by cobalt after sublethal total body roentgen irradiation; the rats were given 250 or 350 r in a single dose and afterwards treated with daily cobalt injections. Cobalt-treated animals showed a rapid recovery of erythropoiesis in contrast to the controls which were similarly irradiated.

These animal experiments inspired the present investigation of the value of cobalt in the treatment and prevention of anemia associated with radiotherapy of malignant tumors.

**Material and Methods.** The patients were of both sexes and had various malignant tumors. Carcinoma of the lung and breast were the most common

conditions but certain other malignant growths were also included in the series. These latter included carcinoma of the larynx, tonsil and urinary bladder, hypernephroma, ganglioneuroma, reticular cell sarcoma and malignant goitre. All except four patients were treated with roentgen rays. One patient with carcinoma of the lung, one with carcinoma of the urinary bladder and one with reticular cell sarcoma were treated with tele  $^{60}\text{Co}$ , in addition one patient with carcinoma of the tonsil received tele Ra.

In carcinoma of the lung the roentgen treatment was generally given to 5 fields of  $8 \times 10$  cm, factors 230 kV, 15 mA and 1 mm Cu filter. The daily skin dose was 350 r and a total tumor dose of 5 000 r was usually reached in approximately 40 treatments. In carcinoma of the breast the same kind of irradiation was administered to 4 fields of  $10 \times 5$  cm,  $6 \times 15$  cm,  $8 \times 10$  cm and  $20 \times 24$  cm. The daily skin dose was 350 r but the largest field received only 300 r. The average total amount of irradiation was 2 450 r to the skin, the average period of treatment being 29 days.

Carcinoma of the lung was also treated with tele  $^{60}\text{Co}$ , 300 r being given at 57 sessions to fields of  $6 \times 8$  cm. Carcinoma of the bladder and reticular cell sarcoma were both treated 36 times with 300 r to field areas of  $8 \times 10$  cm. Carcinoma of the tonsil received tele Ra treatment 19 times in doses of 732 r.

The patients were divided into two groups without reference to the diagnosis and any previous operation. Metastases and other changes produced by the tumor had no influence on the basis of division. Only those who gradually deteriorated during the period of treatment were disregarded. There were three such progressions in the whole material.

CCF 37 tablets were administered to the first group of patients daily during the period of irradiation. The other group was given only iron in the form of Ferroncum (Sandoz AG) tablets which contain the same amount of iron (22 mg) as CCF 37 tablets but no cobalt or copper. Four tablets of CCF 37 or Ferroncum were usually administered daily but in a few exceptional cases 6 tablets were given. The anemia treatment was generally started at the same time as the radiotherapy or some days later. Red cell and leukocyte counts and hemoglobin values were checked in the usual way.

## Results

The changes in blood values during radiotherapy are presented graphically. Since carcinoma of the breast and the lung are the commonest conditions in this material each of these is treated separately; the few other tumors are treated together.

Patients with carcinoma of the breast are represented in Fig. 1, in which 1a shows the erythrocyte count and hemoglobin values in 7 patients treated with CCF 37 and 1b the same values in 7 patients who received Ferroncum. There appears to be a significant difference between these groups. In all but

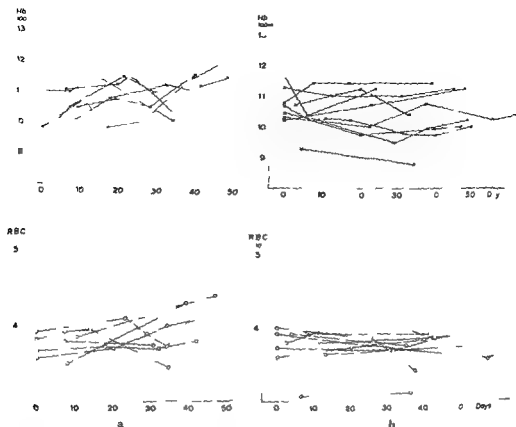


Fig. 2. Diagrams showing the erythrocyte counts and hemoglobin values respectively in 7 patients with carcinoma of the lung treated a) with CCF 37 (tablets) b) with Ferronicum.

one patient treated with CCF 37 a marked elevation of the blood values is evident, in the one patient the values remained at the same level during the treatment. Ferronicum was less effective. There was a lowering of the erythrocyte count and hemoglobin in two patients, and in the others the values remained practically constant or a slight elevation occurred. This was however small as compared with the elevation produced by CCF 37.

Fig. 2 represents the patients with carcinoma of the lung, 7 were treated with CCF 37 (Fig. 2a) and 10 with Ferronicum. The corresponding blood values are given in Fig. 2b. In 5 of the 7 patients CCF 37 produced an elevation of the hemoglobin and the erythrocyte count. In one patient the values remained unchanged and in one a lowering was seen. The Ferronicum treatment was again less effective. An elevation was evident in only 3 patients and in one the values remained at the same level during the treatment. Impairment was observed in 6 patients.

Other tumors form a miscellaneous group and are collected in Fig. 3, with the patients treated with CCF-37 in 3a and those treated with Ferronicum

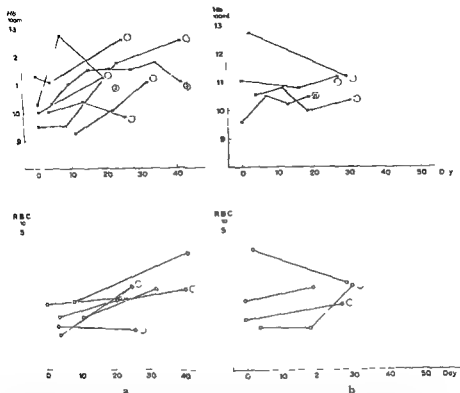


Fig 3 Diagrams showing the erythrocyte counts and hemoglobin values respectively in a miscellaneous group of patients treated a) with CCF 37 tablets b) with Ferronikum. The numbers at the curves indicate the kind of lesion: 1) carcinoma laryngis 2) carcinoma tonsillae 3) hypernephroma 4) carcinoma vesicae urinariae 5) ganglioneuroma 6) sarcoma reticulocellulare 7) carcinoma thyroideae 8) tumor gangliocellulare

in 3b. The diagnosis is indicated beneath each curve by a number the meaning of which is given beneath the figure. Despite the heterogeneity of these tumors and the differences in the radiotherapy, the effect of CCF 37 seemed to be superior to that of Ferronikum.

The leukocyte count was followed in every patient and the development of moderate leukopenia during the radiotherapy was a constant finding. No significant difference in this respect was observed between patients treated with CCF 37 and Ferronikum.

The series is comparatively small and more detailed separation of the different types of cases is difficult so that no attempt was made to calculate relative values. The curves themselves suggest an advantage of CCF 37 over Ferronikum.

Practically no harmful side effects were observed during the treatment. Only one patient treated with CCF-37 had gastric symptoms, these were not severe and may possibly have been an indication of radiation sickness. Six tablets of CCF 37 daily seemed to be more effective than four and the three patients who received this larger dose seemed to tolerate it without difficulty. No further effect was obtained by increasing the dose of Ferronicum to 6 tablets daily.

### Discussion

Many etiologic factors are involved in the development of anemia in patients with malignant tumors subjected to radiotherapy. The role of the tumor, and the secondary changes produced must first be considered. The injurious effect of ionizing radiation on the bone marrow is also of primary importance. It is not always easy to decide which is the main factor responsible. Many of the patients in the present material were anemic prior to any kind of irradiation. When radiotherapy was started a gradually developing leukopenia and, in some patients, anemia indicated damage to the bone marrow. Both the tumor and the irradiation must therefore be evaluated as etiologic factors in the present series.

The results clearly indicated that cobalt, copper and iron administered simultaneously had a more favourable effect than iron alone on the erythrocyte count and hemoglobin. It was shown in animal experiments by SAIKKONEN & MARTTINEN (1963) that cobalt given alone is capable of reactivating erythropoiesis after radiation injury; it may therefore perhaps be concluded that cobalt may be useful in the treatment of anemia produced by ionizing radiation. The need of iron is self evident but the part played by copper is not so clear. It may be that the optimal effect of cobalt on the anemia produced by irradiation cannot be obtained until some copper is present, as in other conditions (ROTHLIV et coll 1956). This question cannot be answered from the results of the present preliminary study. It seems, however, that cobalt plays the main role in promoting red cell production.

It must be emphasized that cobalt is a toxic substance and little is known about its mode of action, facts that restrict its general employment. Many side effects may occur and include disturbances of growth, anorexia and vomiting, claudication and angina pectoris and the development of goitre (REINOLD 1958). Relatively large doses of cobalt reduce the weight of test animals (STANLEY et coll 1947) and produce adrenal hyperplasia (ISSIER 1958), other stress reactions as well as porphyria-like also occur (SAIKKONEN 1959). Much depends on the dosage, however, and it seems that a polycythemic reaction is not desirable during the treatment. It is too early to recommend the general use of cobalt but the results are promising and indicate that there are new possibilities of stimulating the bone marrow after radiation injury.

### Acknowledgement

The authors are greatly indebted to Mr Konradin Kreuzer of Sandoz AG, Basel, for placing CCF 37 and Ferroncum at their disposal.

### SUMMARY

Patients with carcinoma of the lung and breast and certain other malignant tumors were treated with cobalt, copper and iron during radiotherapy to prevent anemia. One group of patients was given the full treatment while the other group received only iron. The effect of the three substances given together was superior to that produced by iron alone.

### ZUSAMMENFASSUNG

Patienten mit Karzinom der Lunge, Mammakarzinom und anderen malignen Tumoren wurden während der Tiefenbestrahlungsbehandlung mit Dosen von Kobalt, Kupfer und Eisen behandelt, um Anaemie zu verhindern. Eine Gruppe erhielt alle diese Elemente, während eine andere Gruppe nur Eisen bekam. Die erste Gruppe zeigte bessere Resultate als die Gruppe, die nur Eisen erhielt.

### RÉSUMÉ

Des malades atteints de cancer du poumon ou du sein ou de certaines autres tumeurs malignes ont subi au cours de la radiothérapie un traitement par le cobalt, le cuivre et le fer pour prévenir l'anémie. Un groupe de malades a reçu le traitement complet et l'autre seulement le fer. L'effet de ces trois corps administrés simultanément a été supérieur à celui du fer seul.

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## PRESERVATION OF OVARIAN FUNCTION IN EARLY CERVICAL CANCER AFTER SURGICAL LIFTING OF THE OVARIES AND RADIATION THERAPY

by

CARL KREBS, N. BLIXENKRONE MØLLER and VIBERT MOSENIUS

The preliminary results obtained in our efforts to preserve ovarian function in young women with early cervical cancer were published five years ago (3, 4). The patients were first subjected to an operation in which the ovaries were lifted up from their normal site in the lesser pelvis and fixed as high as possible in the abdomen, great care being taken in leaving the blood supply intact. Radiation therapy was given in the usual way after healing of the operation wound.

Loss of ovarian function interferes so seriously with the life of young women that great effort should be made to avoid its occurrence. On the other hand, the prognosis of advanced cervical carcinoma is so grave that the paramount consideration must be to give as effective treatment as possible.

BATTEA & BROWN (1956) reported a case in which an attempt was made to preserve ovarian function by ensheathing the ovaries in lead shells before radiation therapy was administered. A large number of cases has also been described in which surgical removal of the uterus was performed, while one or both ovaries were retained. One of the first reports on this type of operation was published in 1938 by McCALL, KEATY and THOMPSON of Louisiana.

An analysis of the results obtained in patients treated since 1949 is presented in this paper. It is accompanied by a brief description of the surgical technique and an estimation of the radiation dose delivered to the ovaries in their normal positions and when lifted and fixed surgically as far away from the uterus as possible.

The first operations were performed in 1949—1950 but there was some hesitancy to continue the therapeutic experiments until it was seen how the first patients fared. In view of the experience gained in hormone dependent genital cancers involving for example the breast or prostate, there was doubt as to what effect the preserved ovarian function and the continued production of ovarian hormones would have on the prognosis of carcinoma of the cervix uteri if the experiments proved successful. It was essential to establish whether a preserved ovarian function would be beneficial detrimental to the result of treatment of cervical cancer, or without significance.

Nine of the first patients of 1949—1950 in stage I and under 40 years were given radium therapy alone after surgical ovarian lifting. Eight were alive after 7 years without signs, while recurrence in the ninth shortly after the termination of treatment was followed by death within the first 12 months. Menstrual function was preserved in 6 of these 8 patients one became pregnant but abortion occurred at the third month.

It may be mentioned for comparison that during the preceding two years (1948—1949) a total of 24 patients under 40 years of age with cervical carcinoma stage I had been treated with combined radium and roentgen irradiation at the Radium Centre. Eighteen of these were alive after 6 years while 6 had died. After the lapse of 7 years another patient had died and the growth had recurred in one. A cure was thus obtained in two thirds of cases (in 16 out of 24). In none of these patients was the menstrual function preserved.

Ovarian lifting was also performed in six patients in stage II and in three patients in stage III. These were given combined radium and roentgen treatment. The beam was as far as possible directed to the parametrium in an attempt to avoid irradiation of the ovaries. Menstrual function was not preserved in any of these patients.

Of the 6 patients in stage II and the 3 in stage III 4 and 1 patients respectively were well and alive after 7 years. These figures are small but they do not seem to suggest that lifting of the ovaries reduces the possibility of cure.

Inferior midline laparotomy was performed following a complete clinical examination. The ligament of the ovary was divided and the ovary with the infundibulo pelvic ligament was mobilised care being taken to leave the blood supply intact. The ovary was then lifted and sutured to the margins of a small incision in the parietal peritoneum of the psoas muscle or retroperitoneally to this muscle so that the ovary occupied a position above the ileopectineal line. The distance between the growth in the portio and the lower pole of the ovary was usually 13 to 15 cm in a few cases up to 18 cm. The fallopian tube



was removed only in a few cases, and usually if it presented signs of chronic inflammation.

Unilateral lifting of the ovary was performed in 7 and bilateral lifting in the remaining cases. Bilateral ovarian lifting has invariably been performed since 1957—1958.

Radium therapy was instituted five to eight days following the operation. Such treatment given in the usual manner will deliver about 3 600 r in 24 hours to the normally placed ovaries. If, as in the present series, the ovaries are moved a distance of about 14 cm, the dose will be reduced to about a fortieth, i.e. to about 90 r in 24 hours.

The treatment was resumed in 1957 following a survey of the 1949—1950 series, and an analysis of the entire series is now presented.

Many questions arise in the treatment of young women for carcinoma of the cervix uteri. The general physical condition of the patient must be carefully considered and attention given to the menstrual function and the sex life as well as to the condition of the vagina. Two interesting studies on osteoporosis published by MEIGS (1958) and FRASER & KING (1958, p. 388) should be mentioned at this stage. These authors concluded that abolition of ovarian function results in osteoporosis 15 to 20 years later. A woman undergoing castration at the age of 20 will, when 40 years old, have advanced in bone age to 60 or 70 years.

### Clinical series (1957—1958)

A total of 35 women whose ages ranged from 23 to 39 years were treated with bilateral lifting of the ovaries followed by radium irradiation alone. Recurrence was recorded in 10 cases, or 28.5%.

This figure was compared with the frequency of recurrence calculated after the same observation period in patients of the same age group from the immediately preceding five year period. This was 32.8% (i.e. 23 out of 70). In spite of the fact that these 70 patients had been given combined radium and roentgen treatment, the percentage of cures obtained after ovarian lifting and radium irradiation does not seem to have been reduced.

Among the 10 patients with recurrence after ovarian lifting malignancy was evident in two after childbirth (which is always a serious complication), a

#### Ovarian lifting

35 patients 10 recurrences

#### Recurrence

1 died within first 9 months	3
1 " " " 10 "	6
1 " " " 3 years	9
7 alive by 3 years with recurrence	28.5

#### Control series

70 patients 23 recurrences

#### Recurrence

2 died within first 3 months	3
2 " " " 6 "	5.7
8 " " " 12 "	11
7 " " " 2 years	37.8
3 " " " 3 "	
1 death has subsequently occurred	

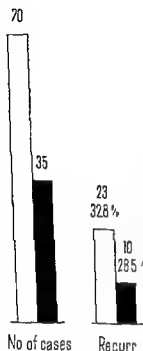


Fig 1 Number of patients and of recurrence in the control series (Ra + roentgen) (white columns) and in patients pretreated with ovarian lifting (+ roentgen) (black columns)

third patient was in stage II and a fourth had a strong familial predisposition (her father and a sister had died of cancer)

These observations may very well serve as a pointer indicating the type of patient in which radium therapy alone will not be sufficient

A more detailed survey of the times of recurrence within the first three years in the two groups is given below

It is possible that some of the patients in the control series classified as stage I had more advanced growths. Ovarian lifting was actually performed in 37 patients but two were excluded because operation revealed that the condition was far more advanced than had been assumed at the vaginal examination. These figures suggest that the margin of error in vaginal examination performed even by experienced examiners may be about 5%.

**Menstruation** It is well known that many conditions including surgical intervention may result in abolition of menstrual function either permanently or temporarily and it would therefore be reasonable to assume that operation on the ovaries might produce this change.

Among the 25 patients without cancer treated with ovarian lifting 19 menstruated normally afterwards although menstruation did not occur for a year in a few and for two years in one patient.

With one exception the 6 patients in whom menstruation did not return were over 34 years of age while menstrual function was re established in 8 patients who were over this age.

One patient became pregnant and aborted at the third month in the series from 1957—1958.

The desirability of performing tubal resection at the time of ovarian lifting has been carefully considered but not as yet accepted. One patient was asked to record the body temperature regularly and the chart distinctly showed the occurrence of ovulation since then the temperatures of all patients have been recorded.

**Sexual function** One of the principal purposes of this study was to investigate if it was possible to preserve a normal sex life.

Eighteen of the 25 patients without recurrence stated that their sexual

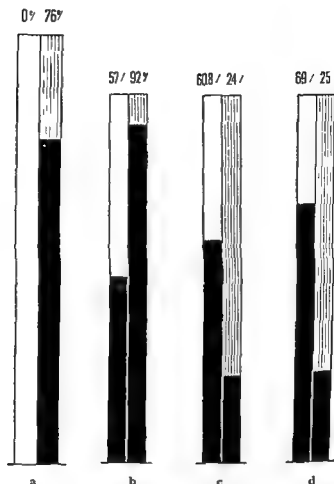


Fig 2 a) Frequency of preserved menstruation. No patients with preserved menstruation after combined radium roentgen treatment in the control series (white column). Preserved menstruation in 76% of patients pretreated with ovarian lifting (black column). b) Frequency of unaltered or improved sexual function in the control series (black column left) and in patients pretreated with ovarian lifting (black column right). c) and d) Frequency of hot flushes (c) and of weight gain (d). Control series (black columns left) and in patients pretreated with ovarian lifting (black columns right).

function was as normal as before the operation both as far as libido and frequency of intercourse were concerned. Four others stated that dyspareunia had been present before the operation, and that no change had occurred, i.e. the conditions were unchanged in 22 out of 25 patients.

One patient seemed to have derived benefit from the intervention in that her previous fear of becoming pregnant had disappeared. Two patients, aged 37 and 38, reported that libido had disappeared after the treatment.

Forty seven of the 70 patients of the control group were symptom free (frequency of recurrence 32.8 %). Information as to sexual function was available for 42 of these 47 patients. Twenty four stated that no change had occurred, 4 had ceased to have sexual relations for fear of recurrence. 11 reported a definite deterioration, and 3 could give no worthwhile information.

*Depth and degree of moisture of the vagina* The significance of measuring the depth of the vagina was unfortunately not appreciated at the beginning of the investigation but the vaginal depth was measured after treatment in two groups in which ovarian lifting or castration had been performed. In none of the patients in the first group did vaginal shortening amount to more than 50 %.

The depth of the vagina in patients undergoing ovarian lifting or castration was as follows:

	Average	Maximum	Minimum
After ovarian lifting	10 cm	12 cm	8 cm
After castration	7 »	10 »	1 »

The vaginal mucosa was normal being moist, non atrophic and folded. It was unaffected by the treatment in the 19 patients with preserved ovarian function.

The vaginal mucosa was studied in 40 of the patients in whom castration had been performed. It was dry and atrophic in more than 60 %, and dry and agglutinated in 10 % of these patients.

*Weight gain* Weight gains were smaller in the patients who had undergone ovarian lifting than in those subjected to combined radium and roentgen irradiation (castration). Among the 42 patients treated with radium and roentgen irradiation in whom menstruation failed to reappear, definite weight gains were observed in 29 (or 70 %) including 5 in whom the gains exceeded 5 kg.

Weight gains were observed in 25 % of the patients treated with ovarian lifting but did not exceed 5 kg in any of the patients. The fatty tissue increase was especially marked on the abdomen and thighs.

*Postmenopausal symptoms* Six (or 24 %) of the patients who had had ovarian lifting complained of hot flushes while 19 had no postmenopausal symptoms. Flushes occurred in 32 (or 76 %) of the 42 patients in the control series. i.e. they were three times as frequent as after ovarian lifting.

It may be mentioned with regard to complications that two patients of the entire series (1949—1950 and 1957—1958) had to be subjected to a second operation for unilateral ovarian cysts.

### Conclusions

Ovarian function was preserved in 25 out of 32 patients aged from 23 to 39 of the entire series with carcinoma of the cervix uteri after lifting of the ovaries.

from the field of irradiation and their fixation at a higher level. The possibility of preserving ovarian function, an intact vagina, and normal tonus of the breasts as well as ensuring a normal sex life with this type of operation must constitute an important factor from the aspect of the welfare and happiness of the patient.

Two (one from 1949 and one from 1957) of the 42 patients became pregnant and aborted at the third month. It must consequently be assumed that the chances of a successful termination of pregnancy are poor.

## SUMMARY

Attempts were made to preserve the ovarian function in young women with cervical carcinoma stage I by lifting the ovaries and attaching them to the parietal peritoneum on the psoas muscle or retroperitoneally to this muscle before radium irradiation. The attempt proved successful in 25 of 32 patients aged from 23 to 39. The possibility of a normal sex life was considerably increased.

## ZUSAMMENFASSUNG

In Fällen von Cervixcarcinom im Stadium I wurde versucht die ovarielle Funktion zu behalten indem man die Ovarien heraufzog und sie am parietalen Peritoneum des Psoas oder retro-peritoneal hinter diesem Muskel befestigte bevor Bestrahlung stattfand. Diese Versuche bewahrten sich gut in 25 von 32 Patientinnen im Alter von 23 bis 39 Jahren. Die Möglichkeit eines normalen Geschlechtslebens war erheblich verbessert.

## RÉSUMÉ

Les auteurs ont essayé de préserver la fonction ovarienne de jeunes femmes atteintes de cancer du col au stade I en fixant leurs ovaires en position haute au péritoine parietal du psoas ou sous le péritoine à ce muscle avant curiethérapie. Ces essais ont été suivis de succès chez 25 femmes sur 32 âgées de 23 à 39 ans. La possibilité d'une vie sexuelle normale a été considérablement augmentée.

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## EFFECTS OF ROENTGENRAYS ON THE ENZYME SUBSTRATE (LUCIFERASE-LUCIFFRIN) SYSTEM OF THE CRUSTACEAN CYPRIDINA

by

W LOHMANN C F FOWLER and W H PERKINS

Both the site of the primary cellular lesion and the earliest physiological changes produced in animals by ionizing radiation have been investigated for several years. Most of the recent studies deal with alterations in the membrane permeability of certain intracellular structures (KAPLAN 1955). The increase in the activity of several enzyme systems observed after irradiation may be due to changes in membrane permeability. BACQ & ALEXANDER (1961) have postulated that enzymes are released from membranes and intracellular surfaces by radiation. Physiological changes then would be produced by the liberated enzymes. DNA however is very radiosensitive while DNAase cannot be liberated by small doses of radiation (OKADA et coll 1957).

Other possible explanations for the increase in enzyme activity observed after irradiation might be (1) a substrate is rendered more susceptible to enzyme action or (2) substrates are partly destroyed leaving unused enzymes to accumulate.

To obtain some information about the relative radiosensitivities of an enzyme and its substrate we have done in vitro studies on the effect of radiation on the

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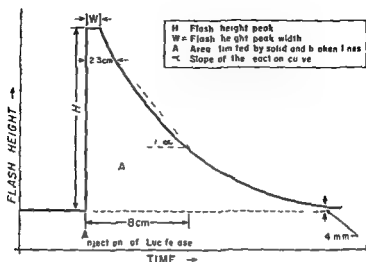


Fig. 1. Schematic figure for explaining the abbreviations used in text and figures.

enzyme substrate (luciferase-luciferin) system of the small ostracod *Cyprina*. This system is an excellent one because both the enzyme and the substrate are in highly purified states and can be irradiated separately.

**Material and Methods.** In these experiments an RCA type 6217 phototube with a range of highest response from 3500 to 6000 Å and a Moseley X-ray chart recorder were used. The negative voltage to the phototube was obtained from a Baird atomic model 312A super-stable high voltage supply. The phototube as well as a test tube with fixed geometry relative to the phototube were in a light tight box.

All irradiations were done with a beryllium window roentgen tube (Philips Electronics Instruments Mt. Vernon, N.Y.) operated at 100 kV and 12 mA and producing a dose rate of  $9 \times 10^4$  r/min.

Four hundred micrograms of highly purified luciferin were dissolved in 4 ml of methyl alcohol. In this solution pure luciferin is relatively stable. The luciferase solution consisted of 400 µg of enzyme dissolved in 4 ml of 0.1 M phosphate buffer. Twenty-five lambda samples of the luciferase solution were pipetted into a small lucite container and irradiated with different doses of roentgen rays ( $3000$  to  $4.5 \times 10^4$  r).

After irradiation, the sample was diluted to 10 ml with 0.1 M phosphate buffer at pH 7.0 making a final concentration of 0.25 µg/ml. Also 25% of the methanolic luciferin solution were diluted to 10 ml with 0.1 M phosphate buffer producing a final concentration of 0.25 µg luciferin/ml.

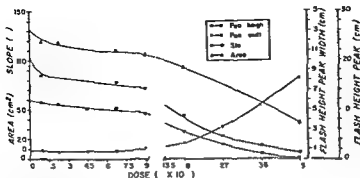


Fig 2 Flash height peak area slope and peak width of the *Cypridina* luciferase-luciferin system as a function of the roentgen dose given to luciferase

First 10 ml of the buffered luciferin solution were poured into the test tube inside the light tight box. The reaction was then initiated by injecting rapidly with a hypodermic syringe, 10 ml of the  $25 \mu\text{g/ml}$  buffered, irradiated luciferase solution.

To demonstrate the effect of the radiation on luciferin, 25  $\mu\text{l}$  of the 0.1 mg/ml methanolic luciferin solution were irradiated under the same conditions as the luciferase. After diluting to 10 ml with 0.1 M phosphate buffer, the solution was poured into the test tube and mixed with unirradiated luciferase solution (10 ml) using the method mentioned above. The total light emitted (area under the curve), the slope of the reaction curve, the flash height peak and the flash height peak width as illustrated in Fig 1 were determined immediately after mixing the enzyme and the substrate.

Unirradiated control samples were used with each particular experiment. Autooxidation could not be observed during the time measurements were made. All measurements were made at room temperature.

### Results and Discussion

The distribution of the values of flash height peak area slope and peak width for luciferase as a function of the roentgen dose is shown in Fig 2. Each individual point represents the mean of several experiments. As can be seen, the enzyme is very radioresistant. There is only a slight change in the activity for doses up to about  $10^5 \text{ r}$ . For higher doses the peak height and the slope decrease simultaneously. The area, however, decreases at a much slower rate. The total light emitted is reduced by only about 50% after irradiation with  $3.6 \times 10^5 \text{ r}$ . This is probably not due to an influence of the concentration of the enzyme, as will be shown later on. Related to this might be an increase in the peak width of about 800% after irradiation with  $3.6 \times 10^5 \text{ r}$ .



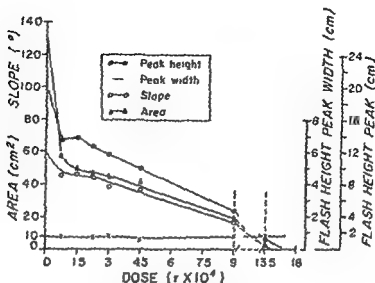


Fig. 3 Flash height, peak area, slope, and peak width of the *Cypridina* luciferase-luciferin system as a function of the roentgen dose given to luciferin.

The results obtained by the irradiation of luciferin are shown in Fig. 3. In this case, the area, the slope, and the peak height decrease almost at a constant rate within experimental error, but the peak width remains constant. A dose of about  $13.5 \times 10^4$  r destroys almost completely the substrate.

In Figs. 4 and 5 the flash height peaks and the areas, as obtained after the irradiation of luciferase and luciferin, are compared. The curves were normalized in the control values. As can be seen, the enzyme is much more radioresistant than the substrate.

To demonstrate the effect of the concentration of either enzyme or substrate on the peak height, the slope, and the area, different amounts (5 to 40  $\mu$ ) of unirradiated luciferase or luciferin solution were mixed together in the test tube. The results are shown in Fig. 6. The peak heights decrease proportionally with decreasing total amounts of either enzyme or substrate. The experimental results are fitted by a straight line and can be represented by the equation  $y = 1.17x$ . By using half the initial amount (20  $\mu$ ) only, the peak height is reduced by half. A straight line could also be obtained for the area in case of adding different amounts of luciferin to 40  $\mu$  of luciferase. There was, however, no linear decrease in the area with decreasing volumes of luciferase and a constant amount of luciferin (40  $\mu$ ). A reduction of about 50% in the amount of the enzyme changed only slightly the total light emitted. The observation can account for the effect mentioned earlier and shown in Fig. 2. Irradiation of luciferase required  $3.6 \times 10^5$  r to reduce the total light emitted by 50%. The

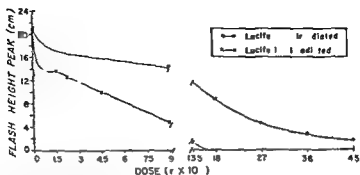


Fig 4 Flash height peaks of the *Cypridina* luciferase luciferin system as a function of the roentgen dose

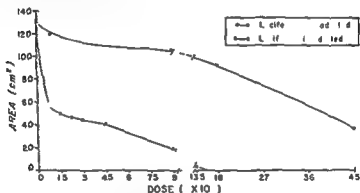


Fig 5 Area (totally emitted light) of the *Cypridina* luciferase luciferin system as a function of the roentgen dose

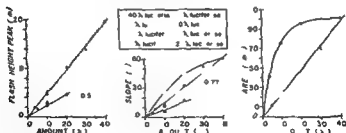


Fig 6 Flash height peak area and slope of the *Cypridina* luciferase luciferin system as a function of the quantity of each constituent

decrease in total light emitted is not proportional to a decrease in enzyme concentration. However, the decrease in the flash height peak is proportional to the reduction in enzyme concentration and can be used as a measure of radiation effect on the enzyme.

The substrate, luciferin, appears to be more radiosensitive than the enzyme, luciferase. A 50 % reduction in the total light emitted is produced by less than  $1 \times 10^4$  r when given to luciferin. However, the same amount of reduction in total light emitted produced by irradiation of luciferase requires about  $30 \times 10^4$  r.

A reduction in luciferase concentration of about 75 % is measured by total light output, is required to decrease total light output by 25 % using non irradiated samples. Thus, a large amount of luciferase would have to be destroyed by irradiation before significant loss of activity could be found, using the area determination.

The flash height peak is a linear function of the quantity of luciferase present. If the flash height peaks are used as criteria for radiosensitivity, luciferase is 3 to 4 times more radioresistant than luciferin, as determined by the 50 % reduction in flash height peaks of the reaction curves.

### Acknowledgements

We appreciate the generosity of Drs F. H. Johnson and Shimoura (Princeton University) in furnishing us with luciferin and luciferase and for their valuable advice. The technical assistance of Mike Fbert and Miss Luanne Strickland is gratefully acknowledged.

### SUMMARY

Twenty-five lambda of practically pure luciferase solution (0.1 mg/ml of 0.1 M phosphate buffer) or 25 lambda of highly purified luciferin solution (0.1 mg/ml of methyl alcohol) were irradiated with different doses of roentgen rays (3 000 to  $4.5 \times 10^5$  r). The initial flash height peak, the slope of the reaction curve and the quantity of light emitted after combination of enzyme and substrate were determined using photocell equipment. The results of these *in vitro* experiments show that the substrate is much more radiosensitive than the enzyme.

### ZUSAMMENFASSUNG

Funfundzwanzig lambda von praktisch reiner Luciferase-Lösung (0.1 mg/ml einer 0.1 M Phosphatpuffer-Lösung) oder 25 lambda einer hochgereinigten Luciferin-Lösung (0.1 mg/ml Methylalkohol) wurden mit verschiedenen Röntgendosen bestrahlt (3 000 bis  $4.5 \times 10^5$  r). Das anfängliche Maximum der Abfall der Reaktionskurve und die nach Kombination von Enzym und Substrat freier werdende Lichtmenge wurden mittels einer Photozelle bestimmt. Die Ergebnisse dieser Versuche *in vitro* zeigen, dass das Substrat wesentlich strahlenempfindlicher als das Enzym ist.

### RÉSUMÉ

Vingt-cinq lambda d'une solution pratiquement pure de luciférase (0.1 mg/ml de 0.1 M phosphate tampon) ou 25 lambda de solution de luciférine très purifiée (0.1 mg/ml d'alcool méthylique) ont été irradiés par différentes doses de rayons roentgen (3 000 à  $4.5 \times 10^5$  r). La hauteur de l'éclair initial, la pente de la courbe de réaction et la quantité de lumière émise après la combinaison de l'enzyme avec le substrat ont été mesurées avec un équipement à cellule photo-électrique. Les résultats de ces expériences *in vitro* montrent que le substrat est beaucoup plus radiosensible que l'enzyme.

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## SIMIL-PORTABLE WHOLE BODY COUNTER FOR CESIUM 137 AND OTHER GAMMA EMITTING ISOTOPES

by

Y. NAVFRSTEN, R. C. MCCALL and K. LIDÉN

After the discovery of the unusually high  $^{137}\text{Cs}$  burdens in Swedish Lapps (LIDÉN 1961) it was realized that a large group of people had to be studied to assess the actually existing contamination levels. Since the people to be measured were about 1700 kilometers from the iron room whole body counting facility (IRC) at Lund and since the Lapps are not easily available for long distance travelling it was decided to design and construct a whole body counter suitable for transport to Lapland.

The whole body counter was designed around the following specifications

1. It should be semi portable i.e. two men should be able to assemble or disassemble it for transport in a few hours.
2. It should have the same geometry as the 42 cm chair arrangement in the stationary whole body counter at Lund (CENFRQUIST & LIDÉN 1962).
3. The detector should be a 5" in diam by 4" thick  $\text{NaI(Tl)}$  crystal.
4. Shielding must be presently available material i.e. lead bricks, the amount of shielding must be minimized to facilitate transport.
5. It must be structurally safe.

It was expected that the Lapps would have  $^{137}\text{Cs}$  body burdens in the range of  $0.1 \mu\text{C}$   $^{137}\text{Cs}$  or more. With such a relatively large amount of activity it was not necessary to have a very low background. We were also of the opinion that

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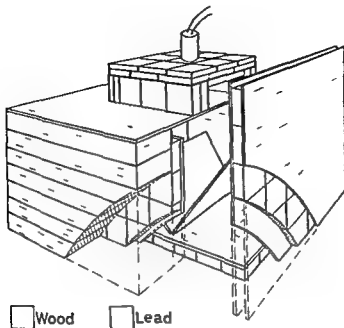


Fig 1 Sem portable whole body counter. The shielding is supported by a structure of 8 x 4 timbers and plywood sheets

determination of the body content of potassium was of a second order of importance

There was very little experience to draw upon in the literature ROESCH et coll 1961 PALMER 1962 and INDELL 1962 have done some work with simple shields

*Description of the whole body counter* A stable basic structure of 8 x 4 timbers made with a plywood roof (Fig 1). A lead floor 4 cm thick is then laid. The wooden structure is used to support side wall of lead 4 cm thick with an inner retaining wall of plywood. A section of the plywood is cut out and replaced by a 4 mm lucite sheet in the area where the subject must pass to reach the detector. The detector 3 inch in diameter and 4 inches thick NaI(Tl) crystal rests upon this sheet of lucite. A small house of lead the walls and roof of which are 8 cm thick is built around three sides and above the top of the crystal. The fourth side must be open in order to let the  $\gamma$  rays pass from the head and shoulders of the subject to the crystal. In order to strengthen the plywood roof a 30 mm by 30 mm by 5 mm right angle iron beam is added at the head end of the plywood roof. A lead wall 4 cm thick held in position by two sheets of plywood is built immediately behind the subject to close the partition.

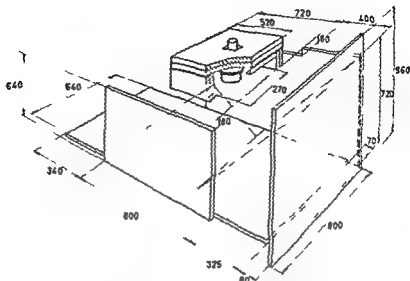


Fig 2 Arrangement of the lead shielding of the semi portable whole body counter. The position of the chair is indicated by dashed-dotted lines

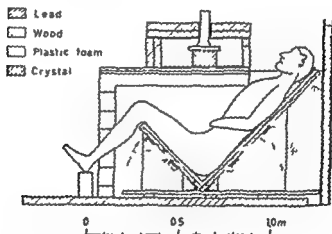


Fig 3 Profile view showing the geometry of the semi portable whole body counter. The principle of the sliding chair is indicated by arrows and dashed lines. The lead shield of the side walls of the counter is not shown. The crystal rests on a lucite sheet replacing the plywood area inside the lead cave.

The arrangement of the lead shielding of the semi-portable whole body counter (PC) is shown in Fig 2. The weight of the shield is about 1200 kg. The total weight of 1500 kg is small enough that most floors can easily stand the counter without further support.



Fig 4 The semi portable whole body counter seen from two different directions with a child in measuring position. The bags containing 5 kg of sugar are used for background measurements

It was decided to avoid using a door since this would greatly increase the complexity of construction. The outer dimensions of the counter thus constructed are only 160 cm (length) by 120 cm (width) by 110 cm (height). This small size was made possible by using a folding chair of plywood sheets (Fig 3). The subject walks into the shield and sits down on the chair, which is folded flat on the floor. The chair is then erected to the standard chair position until the subject sits comfortably in a well defined geometry. Since the head of the subject protrudes out of the shield (Figs 3 and 4) there is no problem of claustrophobia.

*Factors influencing the background* Background studies made at our laboratory showed that additional lead would decrease the background only slowly in comparison to the amount of shielding needed. We have estimated the unshielded openings in different directions according to Table 1 to be about 20 % of full solid angle  $4\pi$ . The measured reduction of the total background counting rate was also about 80 %.

Of those openings mentioned in Table 1 (see also Fig 2) only the first one by closing it could reduce the background to the expense of a reasonably small amount of lead. Measurements at our laboratory showed that a lead shield, 4 cm thick above the stem of the photomultiplier could reduce the background of the  $^{137}\text{Cs}$  energy band (0.60 to 0.72 MeV) and the potassium energy band (1.38 to 1.56 MeV) with 5 and 10 % respectively.

The improvement by adding a lead wall 4 cm thick at the foot end of the counter was also investigated. A wall 64 cm wide and 48 cm high suppressed the background of the  $^{137}\text{Cs}$  energy band by about 7 % and the background of the potassium energy band by about 6 %.



Table 1

*Location of unshielded parts of the counter and their size in per cent of the full solid angle  $4\pi$  (as seen from the crystal)*

	°
The opening for the stem of the photomultiplier above crystal	3
The entrance of the counter	3
The upper part of the side walls	4
The foot end of the counter	6
The head end of the counter	3
All openings	19

Table 2

*Background of the semi portable whole body counter on different locations*

Location	cpm in the energy bands		Background ratio (II/I)
	I 600 to 720 keV	II 1380 to 1560 keV	
No 1	280	230	0.82
" 2	650	530	0.82
" 3	410	330	0.80
" 4	180	120	0.67
" 5	29	13	0.45

*Place No 1 Lund (55.7° N 14.6° E) Sweden* The counter in the middle of an air conditioned room room dimensions about  $10 \times 5 \times 2$  m<sup>3</sup> floor about 2 m below ground level concrete walls ceiling and floor

*Place No 2 Jäkkmökkt (66.6° N 19.9° E) Sweden* The counter in the middle of a room of the following approximate dimensions  $4 \times 3 \times 2$  m<sup>3</sup> floor about 2 m below ground level concrete walls ceiling and floor

*Place No 3 Jäkkmökkt (66.6° N 19.9° E) Sweden* The counter in the middle of a room close to that of place No 2 room dimensions about  $6 \times 6 \times 2$  m<sup>3</sup> floor about 2 m below ground level concrete walls ceiling and floor

*Place No 4 Inari (68.9° N 27.0° E) Finland* The counter in the middle of a room in a wooden house room dimensions about  $5 \times 5 \times 3$  m<sup>3</sup> floor about one meter above ground level

*Place No 5 Lund (55.7° N 14.6° E) Sweden* The detector in an air conditioned iron room 210 cm by 250 cm by 190 cm (height) walls and floor 18 cm thick of laminated iron the ceiling shield consists of 1 cm iron and 8 to 12 cm lead the floor about 2 m below ground level

In such a counter with only moderate shielding the background is very dependent on the environmental radiation. It was expected that our measurements in the laboratory room with concrete walls, ceiling and floor the floor being about 2 m below ground level would in some respects constitute an un-

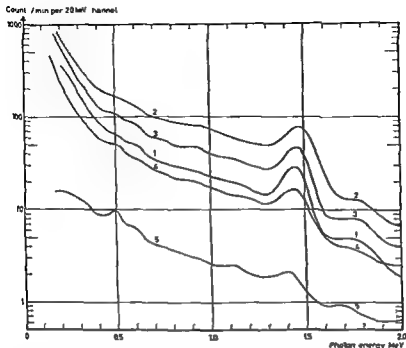


Fig 5 Background spectra in the energy range from 0.2 to 2.0 MeV obtained in the semi portable whole body counter at the four places mentioned in Table 2 compared with the background in a conventional iron room (spectrum No 5). The dominant peak is mostly from potassium in the environment of the counter. Small amounts of radon daughters can be distinguished from various bumps.

favourable background situation. The background should be significantly lower in a wooden house and in a room above ground level.

The backgrounds in Table 2 are measured with a 70 kg non radioactive sugar phantom in the counting position. It can be seen that the background of the PC could vary within wide limits, probably almost exclusively depending on the degree of radioactive contamination in the neighbourhood of the counter. The relation between the counting rate of the  $^{137}\text{Cs}$  energy band and that of the potassium energy band shows that there is a qualitative difference between the various background spectra. The concrete is undoubtedly contaminated with radionuclides emitting high energy gamma rays.

Background spectra as they are obtained at places mentioned in Table 2 are shown in Fig 5. For comparison a background from the IRC is shown too (curve No 5). Backgrounds at places Nos 2 and 3 are definitely elevated, probably due to a higher contamination level of natural radioactivity in the surroundings. The peaks and bumps can be interpreted as gamma rays from dis

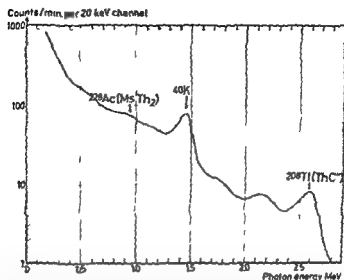


Fig. 6 Background spectrum obtained in the semi portable whole body counter at place No 2. The marked peak at 2.62 MeV and the bump at 0.96 MeV from thorium daughter products to some extent explain the relatively high background at this place.

integrating nuclides of the uranium and thorium series and of  $^{40}\text{K}$ . In Fig. 6 is shown the background from place No 2 in the energy range from 0.2 MeV to 2.9 MeV. Besides the peaks and bumps noticed in Fig. 5, a peak at 2.62 MeV from  $^{208}\text{Tl}$  of the thorium series is visible. The most predominant peak at 1.46 MeV originates from naturally occurring  $^{40}\text{K}$  in the neighbourhood of the detector.

To be able to make accurate whole body radioactivity determinations it is also important to take into account the effect on the background of varying body sizes. Owing to the moderate shielding a sizable amount of background photons will be attenuated in a body placed in the counting position. Some of these will hit the crystal as degraded photons.

Photons which, in the case of empty chair, would not have hit the crystal will be directed towards the crystal by scattering processes in the body. Without passing at least 4 cm of lead, however, only those photons entering through the open foot end of the counter can hit the crystal at a scattering angle of less than  $90^\circ$ . Attenuation by the body of background  $\gamma$  rays of a certain energy therefore will show up as a depression of the counting rate within its full energy peak. A smaller depression occurs in the energy range of its Compton distribution. Superimposed on this depressed background are then the counts from additional degraded photons scattering into the crystal by the object itself, most of them having an energy less than 511 keV.

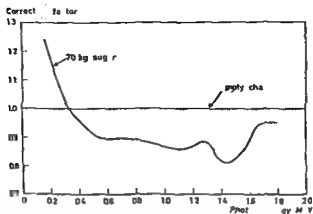


Fig 7 The effect on the background of photon interactions in a large mass in the counting position. The background spectrum of a 70 kg sugar phantom is normalized to a background of empty chair

The effect on the background of varying body sizes has been studied with non radioactive sugar phantoms of several sizes in the counting position of the PC. The phantoms were made in sections of 5 kg sugar bags. They were built to resemble the shape of the body of a human being. The ratio of the background of a 70 kg phantom to that of an empty chair, as a function of the energy is shown in Fig 7. The correlated spectra show the effect of photon interactions in large masses inside the counter. Degraded photons will result in an elevated background counting rate of the channels below 300 keV. Above 100 keV we obtained a markedly decreased background counting rate with a 70 kg sugar phantom in comparison to that obtained without sugar in the counter. This is due to the attenuation in the phantom of photons penetrating the shield.

The background in different energy ranges shows approximately a linear relation to the phantom mass in the region from 30 to 80 kg (Fig 8). The break of the lines of the high energy bands at about 30 kg could be a result of the attenuation of gamma rays from the floor outside the counter. The first 30 kg sugar will obviously more effectively shield the detector from photons passing the lead floor than sugar does thereafter added to get larger phantoms. Below 300 keV, owing to scatter, there is an increasing background counting rate with the phantom size. The counting rate in the total energy range from 0.1 to 1.8 MeV also increases with the phantom size. However, for all energy bands above 400 keV the counting rate decreases with phantom size.

If a standard background is automatically or otherwise subtracted a further correction in order to get a correct net count is easily applied according to the following considerations:

$N_{b\ St}$	= standard background with a phantom weight of $St$ kg	cpm
$N_{b\ x}$	= background for a person with a weight of $x$ kg	cpm
$f_{x\ St}$	= $\frac{N_{b\ x}}{N_{b\ St}}$ = background correction factor	
$N_g$	= gross count	cpm
$N_a$	= $N_g - N_{b\ St}$ = net count before correction	cpm
$N$	= $N_g - N_{b\ x}$ = true net count for a person weighing $x$ kg	cpm
$S$	= sensitivity of the whole body counter	cpm/nc

From these definitions the following formula is deduced

$$N = N_a + N_{b\ St} (1 - f_{x\ St}) \quad \text{cpm (1)}$$

The correction corresponds to a body burden of

$$A_{\text{corr}} = \frac{N_{b\ St}}{S} (1 - f_{x\ St}) \quad \text{nc (2)}$$

At place No 1 the change of the background in the  $^{137}\text{Cs}$  energy band due to different body sizes in the counter, was found to be 0.11 % per kg. If a standard background with a 70 kg phantom is used and if the background is less than 700 cpm (see Table 2) this correction corresponds to less than 10 nc  $^{137}\text{Cs}$  for a subject of 30 kg body weight.

*Calibration of the semi-portable whole body counter for absolute measurements of  $^{137}\text{Cs}$  body burdens.* The whole body counter was constructed to have the same geometry as the 42 cm chair arrangement of the stationary whole body counter at Lund (CEDERQUIST & LIDÉN 1962). Therefore the calibration data of the latter in the first approximation should be applicable to the PC.

However a small correction of the figure of sensitivity had to be made, since the detector in the PC was supported by a lucite sheet, 4 mm thick and the head end of the plywood roof of the counter had a 30 mm by 30 mm by 5 mm right angle iron beam. By a somewhat simplified geometrical consideration it was calculated that the absorption of the  $^{137}\text{Cs}$  and  $^{40}\text{K}$  gamma rays amounted to 5.0 % and 3.4 %, respectively. Therefore the counting efficiencies of these isotopes a priori were assumed to be correspondingly smaller in the PC than in the stationary facility. Using the most recent level schemes of  $^{137}\text{Cs}$  and  $^{40}\text{K}$  (Nuclear Data Sheets 1959 and 1961) the sensitivity of the counter for these radionuclides at equilibrium in a subject of 70 kg body weight is 2.76 counts per minute per nanocurie  $^{137}\text{Cs}$  and 0.180 counts per minute per gram potassium. The uncertainty of these figures is about 5 %.

In order to test the counting efficiency of the PC great efforts have been made to compare it with result in the IRC. Persons measured in places Nos 3 and 4 were transported by car and train to Lund to get comparable measurements as soon as possible. However, it was not possible to arrange it without a delay.

Table 3

Comparable counting rates in the energy range from 0.60 to 0.72 MeV from  $^{137}\text{Cs}$  as obtained with the same detector in the semi portable whole body counter and in the iron room whole body counter at Lund

Subject	Weight of the subject kg	Counting rate		Discrepancy (A-B) cpm	Significance of (A-B) 2 S D cpm
		A in PC cpm	B in IRC cpm		
Y N	72	185	177	8	8
J C	77	240	240	0	11
Y N	72	132	132	0	4
E M	61	900	903	-3	34
T M	34	210	199	11	13

of a couple of days Table 3 shows the result of such measurements of different subjects in the PC and the IRC. The counting rates of the PC have been corrected for 5 % absorption in the detector supporter. All backgrounds used were obtained with non radioactive sugar phantoms of correct weight except for subject T M in the PC. His background obtained with a 65 kg sugar phantom was corrected according to the formula (2) on page 191 using a relative background correction factor of 0.0011. All counting rates are also corrected for contribution of potassium counts in the  $^{137}\text{Cs}$  energy band. A correction is also made on the assumption of a daily excretion rate of 1 %. Table 3 does not indicate any difference in the counting efficiency between the compared whole body counters.

In the PC, children down to about 25 kg body weight were assumed to be measured. Therefore it was desirable to take into account the relation between the counting efficiency and the body weight. The iron room counter was calibrated for  $^{137}\text{Cs}$  in the body for a standard man. The efficiency variation with the body weight was not very particularly studied. With a 7 in diam by 3.5 thick NaI crystal MILLER et coll (1959) have shown that the variation is less than 5 % of the sensitivity of potassium for a change in body weight from 50 to 96 kg. With a 8 diam  $\times$  4 thick NaI crystal MILLER 1962 reported results indicating a variation of the sensitivity for potassium in the body of about 10 % for a change of 50 kg in body weight. In our laboratory using a 5  $\times$  4 NaI (Tl) crystal a decrease in the efficiency of about 10 %, for a change in body weight from 50 to 100 kg has been found.

Measurements of cylindrical plastic containers filled with solutions of  $^{137}\text{CsCl}$  have shown a rather wide variation of the counting efficiency for different parts of the body as could be expected from simple geometrical considerations (Fig 9). Each of the four sections consisting of two cylindrical plastic containers were counted while the other three were replaced by non radioactive sugar

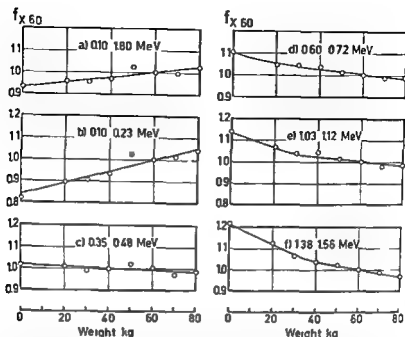


Fig. 8. The background correction factor ( $f_{x 60}$ ) for different energy intervals obtained with several sizes of the sugar phantom. Above 400 keV, due to attenuation, the background decreases with increasing mass. In the low energy part of the spectrum, due to additional degraded photons, the background increases with the phantom mass.

bags. The figures indicate the relative counting efficiency. They show that radioactivity in the lower parts of the legs is counted with a rather low efficiency. By weighing the contribution to the counting efficiency of different parts of the phantom it was possible to get an idea of the variations with body weight below 50 kg. The weight of the different counting efficiencies was obtained from a consideration of both the body size and the distribution of muscles within subjects with body weights of 25 and 50 kg, respectively. This calculation indicates a variation of the efficiency of 0.3 to 0.5 % per kg body weight from 25 to 50 kg, the efficiency being higher for small body sizes.

A direct measurement in the PC of a phantom of plastic cylinders containing  $^{137}\text{Cs}$  solution and resembling a subject of 20 to 25 kg body weight gave a sensitivity which was 19 % higher than that obtained with subjects of standard weight. This corresponds to an average change of sensitivity of about 0.4 % per kg from 25 to 75 kg.

From these considerations a variation of 0.3 to 0.5 % per kg from 20 to 50 kg and 0.2 to 0.3 % per kg from 50 to 100 kg body weight should be a rather good approximation.

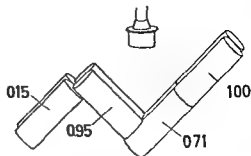


Fig 9 A simple synthesized phantom consisting of 4 compartments of double cylindrical containers. The figures indicate the relative counting efficiency of the different compartments.

Since this counter is constructed for measurements of relatively high body burdens of  $^{137}\text{Cs}$ , the contribution of potassium counts in the  $^{137}\text{Cs}$  energy band is of little importance. These counts should never correspond to more than 4 nc  $^{137}\text{Cs}$ . However, in most normal cases they correspond to about 1 nc  $^{137}\text{Cs}$  for subjects below 50 kg body weight for heavier persons about 2 nc  $^{137}\text{Cs}$ .

The considerations above lead to the following general formula for determination of the body content ( $A_{\text{Cs}}$ ) of  $^{137}\text{Cs}$  in human beings

$$A_{\text{Cs}} = \left[ \frac{\text{cpm}_{\text{c}}}{2.76 [1 + 0.004(70 - w)]} - \begin{cases} 2, & w > 50 \text{ kg} \\ 1, & w \leq 50 \text{ kg} \end{cases} \right] \text{nc } ^{137}\text{Cs} \quad (3)$$

where  $\text{cpm}_{\text{c}}$  is the net counting rate in the interval of 0.60 to 0.72 MeV and  $w$  is the body weight of the subject.

### Counting accuracy

The most important factor determining the accuracy in the evaluation of body burdens of radioactive isotopes is governed by the random occurrence of the pulses. Table 4 shows the statistical accuracy of the determination of body burdens of  $^{137}\text{Cs}$  as indicated by one S.D. in per cent of the number of net counts. The calculation is made on the assumption of counting times from 10 to 60 minutes for body burdens from 5 to 500 nc  $^{137}\text{Cs}$  and for three different background counting rates. The first one corresponds to the relatively high background level at the place No 2 of Table 2. The second background represents a rather good counting situation for the PC at place No 4 of Table 2. For comparison the statistical accuracy of the IRC at Lund is calculated where the background counting rate is about 30 cpm/nc in the same energy band. In all cases the sensitivity is assumed to be 2.76 cpm/nc. From Table 4 it is calculated that the greatest standard deviation for a 10 minute gross count and a 10 minute background count corresponds to about 4 nc  $^{137}\text{Cs}$  independent of the body burden of this isotope. If 2 S.D. is used as a measure of the statistical accuracy, the uncertainty owing to statistical fluctuations is less than 9 nc  $^{137}\text{Cs}$ .



Table 4

The statistical accuracy expressed as one S.D. in per cent of the number of net counts (the calculation is made for a sensitivity of 2.76 counts per minute per nanocurie of  $^{137}\text{Cs}$  and for the same counting time and background)

Counting time min	Background cpm	Body burdens nc $^{137}\text{Cs}$						
		5	10	20	50	100	200	500
10	650	83	42	21	8	5	3	1
	180	44	22	12	5	3	2	1
	30	20	11	6	3	2	1	<1
20	650	59	30	15	6	3	2	<1
	180	31	16	8	4	2	1	<1
	30	14	8	4	2	1	1	<1
60	650	34	17	9	3	2	1	<1
	180	18	9	5	2	1	<1	<1
	30	8	4	3	1	<1	1	0.4

The accuracy in the determination of body contents of  $^{137}\text{Cs}$  is highly governed by the stability of the background which in most cases is a matter of holding the radon concentration at a constant level in the surroundings of the counter. With fluctuating weather conditions the radon concentration is subject to considerable variation. Since the radon daughter products, especially RaC, have several  $\gamma$  ray lines above 0.6 MeV, this varying radon concentration will effect the background counting rate in the  $^{137}\text{Cs}$  energy band. At the places Nos 2 and 4 the maximum deviation from the average of frequently measured 10 minute backgrounds of the  $^{137}\text{Cs}$  energy band was about 2 S.D. This variation was too small to be significantly attributed to varying radon concentration. Therefore with very simple precautions the uncertainty owing to this variation probably should correspond to less than 2 nc  $^{137}\text{Cs}$ .

The superficial radon contamination of the subject itself is a problem of the same nature. The only real cure is a shower for the subject, especially his hair, and a change of clothes before measurements. Without any precautions the superficial radon contamination could result in false counts in the  $^{137}\text{Cs}$  energy band corresponding to several nc  $^{137}\text{Cs}$  in excess of the real body content.

The background depression owing to the subject in the counter also could give an error if the background phantom in its scattering properties does not sufficiently well resemble the subject. The magnitude depends on the background level. In our case this error should not correspond to more than 2 nc  $^{137}\text{Cs}$ .

The correction for potassium counts distributed in the  $^{137}\text{Cs}$  energy band is certainly assessed within 1 nc  $^{137}\text{Cs}$ .

Summed up, a carefully evaluated value of a subject's body burden of  $^{137}\text{Cs}$  from a 10 minute measurement in the PC should not be in error by more than 15%  $^{137}\text{Cs}$ .

It is the opinion of the authors that this simple counter could find applications for medical and other survey purposes, in many cases offering a good alternative to the more complex and expensive whole body counters of the iron room type.

### Acknowledgements

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One of us, R. G. McCall, was supported by a Research Fellowship from the National Cancer Institute, Public Health Service, U.S.A.

### Addendum in the proofs

Recently (in March and April 1963) the counter was used as a mobile unit in a big motor bus. The counter was placed in the middle of the bus. The floor of the counter was about 80 cm above ground level. The mobile unit was used at a distance of less than 20 m from the rooms defined as place No 2 and place No 3 in Table 2. The backgrounds of the energy bands I and II were then 150 cpm and 85 cpm respectively. The background ratio (II/I) was 0.57. At 8 different places along more than a 2 000 km long road from northern to southern Sweden, the background of band I varied from 110 cpm to 230 cpm. The background of band II varied from 65 cpm to 130 cpm and the background ratio from 0.48 to 0.73.

### SUMMARY

A whole body counter for determination of body burdens of  $^{137}\text{Cs}$  and other isotopes is described. The counter easily assembled and disassembled, has small dimensions and the weight is less than 1 500 kg. The background reduction is obtained by lead shielding. The effect on the background of the radioactive environment and of the size of the subject has been studied. The measuring geometry, a  $5 \times 4$  NaI(Tl) crystal in a 42 cm chair geometry, has been calibrated by comparison with a static iron room counter. The sensitivity is 2.76 cpm/mc  $^{137}\text{Cs}$ . The measuring accuracy as a function of body burden and background is analysed.

### ZUSAMMENFASSUNG

Ein Ganzkörperzähler für Bestimmung von  $^{137}\text{Cs}$  und anderen radioaktiven Isotopen im menschlichen Körper wird beschrieben. Der Zähler der leicht auf und abgebaut werden kann, ist verhältnismässig klein und wiegt weniger als 1 500 kg. Die Abhängigkeit des Nulleffekts von der radioaktiven Kontamination der Umgebung und von der Körpergrösse sind studiert worden. Der Ganzkörperzähler mit einem Natriumjodidkristall ( $12.5 \text{ cm} \times 10 \text{ cm}$ ) in 42 cm Stuhlgeometrie ist mit Hilfe von Vergleichsmessungen mit einem stationären

naren Stahlkammerzähler kalibriert worden. Die Empfindlichkeit wurde als 2.76 Imp./min pro nc 137 Cs festgestellt. Die Abhängigkeit der Messgenauigkeit von der Körperaktivität und von der Grösse des Nulleffekts wird analysiert.

## RÉSUMÉ

Les auteurs décrivent un compteur humain total pour la mesure de la charge du corps humain en  $^{137}\text{Cs}$  et en autres isotopes. Ce compteur facilement monté et démonté est de petites dimensions et pèse moins de 1 500 kg. La réduction du bruit de fond est obtenue par un blindage de plomb. L'effet de la radioactivité ambiante et des dimensions du sujet sur le bruit de fond a été étudié. La géométrie du dispositif de mesure, un cristal de NaI (Tl) de  $5 \times 4$  pouces distant de 42 cm du fauteuil, a été étalonnée par comparaison avec un compteur fixe dans une chambre blindée de fer. Sa sensibilité est de 2.76 cpm/nc  $^{137}\text{Cs}$ . L'exactitude de la mesure en fonction de la charge du corps humain et du bruit de fond a été étudiée.

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## DEVELOPMENT OF THE SWEDISH ROENTGEN STANDARD LABORATORY EQUIPMENT

by

R THORAEUS

The free air standard chamber is still the primary instrument for the experimental realization of the international roentgen at radiation energies up to 500 kV. Fully aware of the fundamental importance of having access to such a chamber standard laboratories and many radiotherapy centres have designed and installed such units. In Sweden a complete standard laboratory for measurements of roentgen radiation excited by tube voltages up to 200 kV constant potential was planned and designed in 1929. In 1930 the installation was in operation at our institute (ref 4) and the free air standard chamber then installed is still used as the national standard. Improvements of details have naturally been introduced since then but always in such a way that continuity is maintained. Some of the improvements will now be described.

An increase of the calibration capacity of the standard laboratory above 200 kV was planned by the author at the beginning of the nineteen fifties. With monetary grants from the Government and from the Anti Cancer Society of Stockholm it was possible to order and install an encapsulated high voltage generator capable of 300 kV constant potential, designed to specified qualifications and a 300 kV roentgen tube of special design capable of operating from 6 to 300 kV constant potential with 25 mA at 10 kV and

4 mA at 300 kV. A photograph of this tube is shown in Fig. 1. The electrostatic high tension voltmeter mentioned below is seen to the left and the new generator to the right. The installation was completed in July 1954 and is still in use.

Three different types of instrumentation were at our disposal for measurement of the constant potential tube voltage:

1. A sphere gap with spheres of 30 cm diameter, capable of voltage measurements up to 350 kV.

2. An electrostatic voltmeter of the Abraham Villard type, this can be used from 6 to about 250 kV by overlapping ranges.

3. Two high ohmic oil immersed resistor units in the high voltage generator tanks. The current through these units is measured by a microammeter positioned in the switch table and provided with a scale showing the tube voltage in kV. This instrument has two sensitivity ranges: 0 to 100 kV, and 0 to 300 kV which can be used alternatively.

At the end of 1954, low voltage d.c. high ohmic resistor units were constructed, they were produced by adding a large number of 5 megohm resistors. The resistance of each of them was determined by measurements using a voltmeter and a microammeter, both calibrated with an accuracy of  $\pm 0.2$  per cent, and battery potentials of 250 to 400 volt. Some of the resistors were tested with ten to fifteen different potentials between 40 and 700 volt showing close proportionality between potential and current and thus a satisfactory constancy of the resistance.

The 5 megohm resistors used are tube shaped and can therefore easily be mounted on a perspex rod. In this way two reference resistor units of accurately known resistance were constructed, each about 1 metre in length. Their resistances are 95.74 and 95.60 megohm respectively. They can be used single in parallel, or in series. When not used, the units are stored in closed tubes of laminated paper, thus effectively protected from dust and easily handled.

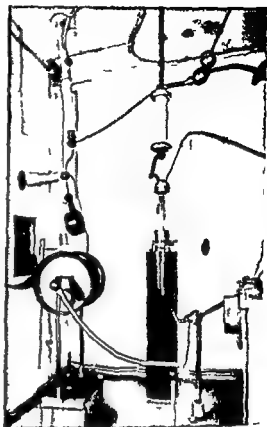


Fig. 1. The 300 kV roentgen tube in the standard laboratory. To the left the electrostatic voltmeter measuring the tube voltage.

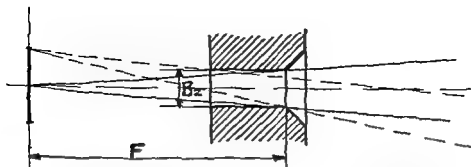


Fig 2 Distortion of beam and plane of definition if the focal size projection on a focal plane perpendicular to the centre line of the beam is greater than the diaphragm diameter

The resistance of each individual resistor of the units can be re checked whenever wanted

The resistance of the two oil immersed high ohmic resistors mentioned above was then determined by current measurements, using battery potentials between 5 000 and 10 000 volt measured by the reference resistor units and a microammeter. The high ohmic resistors are commercially available and nominally of the order of 500 megohm. Another set of two such calibrated oil immersed resistors and a microammeter in the switch table are used for measurement of the constant potential tube voltage obtained from a separate high voltage generator used in operating different types of roentgen tubes for short focal distance therapy.

In a personal communication Dr H O WICKOFF of the NBS Washington has informed the author of a recent paper from the Bureau (ref 2), describing a new design for an accurate d.c. standard resistor similarly made up of a large number of resistors connected in series but arranged to form a vertical helix in air between a ground plate and a high voltage electrode. This resistor unit is designed for direct measurements of high voltages.

For various reasons the roentgen tube of a free air standard chamber installation should have the smallest possible focus size and emit the smallest possible percentage amount of off focus radiation (ref 5). A special reason for using a small focus is illustrated in Fig 2. As may be seen the plane of definition of the diaphragm becomes undefined if the focus size is greater than the diameter of the diaphragm aperture.

The 300 kV roentgen tube in Fig 1 has the focus characteristics indicated by the natural size pinhole photographs in Fig 3. The normally exposed photograph (Fig 3a) shows that the size of the focus spot is about  $5 \times 6$  mm. The photograph in Fig 3b 10 times longer exposed reveals an overexposed focus spot and a small amount of off focus radiation. Both photographs were taken at a tube voltage of 150 kV constant potential without additional filter. The tube wall window (inherent filtration) is of 3 mm thick beryllium.

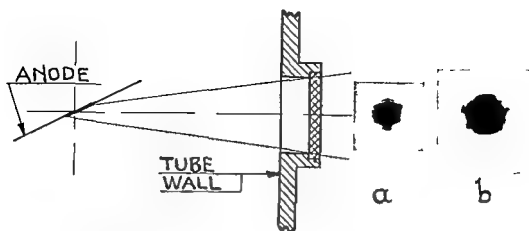


Fig 3 Section through the roentgen tube of the free air standard chamber equipment and natural size pinhole photographs of the focal region

One roentgen of the radiation used produces in a free air chamber a corpuscular emission such that when an arbitrary measuring volume of free, i.e. unrestricted, air at standard atmospheric conditions is irradiated, saturation current and electronic equilibrium conditions prevailing, and the maximum range of the corpuscles being fully utilized, ions carrying one electrostatic unit of quantity of electricity are obtained per cubic centimetre of the irradiated measuring air volume. In the experimental realization of the unit the quantity of electricity collected may readily be measured by a suitable instrumental equipment compared to which the measuring air volume used is usually a number of cubic centimetres, which has to be determined by calculation.

The ionization current measuring system of a free air chamber forms an electric circuit, the stability of which may easily be checked. A constant source of ionization current is then substituted for the ionization in the chamber and the change in potential in the collecting precision capacitor is measured as usual. The ionization current most convenient for this purpose is obtained by using the corpuscular emission (alphas or betas) from a radioactive substance of long half life. A uranium ionization current standard has for a long time been used in our standard laboratory with good result.

One of our collecting capacitors consists of coaxial brass tubes with air as dielectric medium, except at the ends where the tubes are mechanically fixed in position by small amber rings. This capacitor is protected against stray radiation by 3 mm lead + 1 mm brass. It was separately calibrated at three standard laboratories abroad (ref. 9). The values obtained were as follows:

In England (1953)	201.4 $\mu\mu\text{f}$
In Germany (1954)	201.2 $\mu\mu\text{f}$
In U.S.A. (1956)	201.2 $\mu\mu\text{f}$

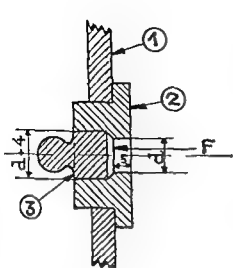


Fig 4 Section through earlier beam-defining diaphragm arrangement 1) Front wall of standard chamber 2) interchangeable diaphragms of different aperture  $d$  3) beam absorbing plug

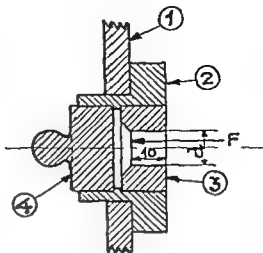


Fig 5 Section through the new beam-defining diaphragm arrangement 1) Front wall of standard chamber 2) diaphragm holder 3) interchangeable diaphragms of different aperture  $d$  4) beam absorbing plug

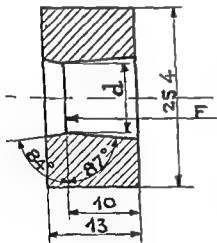


Fig 6 Diaphragm disc in which a lightly coned surface replaces the cylindrical surface

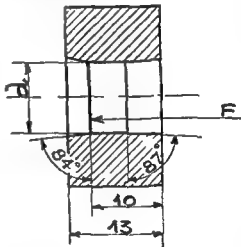


Fig 7 Diaphragm disc in which a lightly coned surface replaces part of the cylindrical surface

It appears that the values are very nearly the same. This shows that the capacitor itself has the high constancy required for the purpose in hand.

In 1956 when the portable Swedish free air standard chamber unit was calibrated at the NBS, Washington, the complete ionization current measuring equipments of the two free air units were directly compared one against the



other (ref 11) An agreement within 0.1 per cent was then found This is in accord with the last ICRU report (ref 1) in which a maximum error of  $\pm 0.1$  per cent is estimated for the charge measuring equipment

The measuring volume is defined by the length of the collector electrode and the geometry of the diaphragm system in relation to the roentgen tube and the collector electrode The length of the measuring volume is geometrically defined by the length of the collector electrode plus the sum of half the spaces between the collector electrode and the adjacent guard electrodes According to earlier experiments in this institute (ref 8) this method of defining the length has been found to hold true for lengths down to 1.5 cm using a space of 0.5 mm at each end of the collector electrode

The cross section of the measuring volume is defined by the diaphragm aperture and the beam geometry The diaphragm system used here, until the middle of the nineteen fifties, is shown in Fig 4 and consists of interchangeable diaphragms of different aperture diameters up to a maximum of 22 mm The beam defining part is a cylindrical hole 5 mm in length, this was considered sufficient to define the beam when tube voltages not above 200 kV constant potential were used The plane defining the cross section of the beam, and the direction of the radiation, are indicated by the arrow F in the figure This diaphragm system was described in detail in a previous paper (ref 7) It will only be mentioned therefore, that the material used was so called hard lead (90 per cent lead and 10 per cent antimony) and that the same system was used with the portable free air standard chamber unit, which was specially designed to be the intermediary medium in the comparison of the Swedish stationary standard chamber with those of Great Britain, Western Germany, and USA (ref 8, 10, 11) and also was used to compare two of the foreign chambers (ref 11)

The use of a lead plug close behind the diaphragm aperture as shown in Fig 4 may be briefly explained This arrangement permits direct measurement of the total leakage correction without introducing modifications or changes of the scattering and other leakage conditions and their geometry It has been used in this standard laboratory for a long time at first in the stationary free air standard chamber and later also in the portable unit when this was used abroad in the period 1953 to 1956 (ref 11) It has been found to be both convenient and reliable The new modified diaphragm arrangement described below (see Fig 5) is particularly convenient as being so simplified that only one plug is required for all the diaphragms

In connection with the increase of the calibration capacity a modified diaphragm arrangement was introduced The cost of this was covered by a separate monetary grant from the Anti Cancer Society of Stockholm This system is shown in Fig 5 and consists of interchangeable diaphragm discs the aperture diameter of which can be up to a maximum of 22 mm, the beam defining part of the discs is a cylindrical hole 10 mm in length

Table 1  
Diameter of our diaphragm No 8a

Diameter	Measurement results in mm		
	Stockholm 1946	Washington 1956	Stockholm 1959
Front	8 00 <sub>5</sub>	7 99080	7 9920
Middle	—	7 99465	—
Rear	(8 00 <sub>5</sub> )	7 99719	7 9945

The material used for the whole system is a Swedish made heavy alloy of tungsten having a density of 18. This material has been found to be excellent for the purpose in question, and easy to machine. The diameter of the incident primary beam at the front surface of the diaphragm holder is always kept within the diameter of that surface (about 50 mm). The plane of definition, and the direction of the radiation are indicated by the arrow F.

The old and the new beam defining diaphragm arrangements may be used alternatively. This enables direct comparisons and thus a complete maintenance of the continuity. In addition the new diaphragm discs are given the same external dimensions as the diaphragm put at the disposal of standard laboratories by the NBS for comparison with their own diaphragms (ref. 1). A direct interchange for this purpose is thus very easy. Furthermore the disc shown in Fig. 5 has the same aperture form as the NBS diaphragm.

As has already been mentioned and illustrated in Fig. 2, a cylindrical diaphragm aperture can be used safely only if the size of the radiation emitting area projected on a plane perpendicular to the centre line of the beam is smaller than the aperture diameter. Therefore, when two diaphragms of different diameters are monometrically compared errors may occur if one or both of the diameters are smaller than that of the radiation emitting area, or if the difference between them is great. It is however evident that this source of error may be eliminated if a slightly coned surface is used in place of the cylindrical surface. A diaphragm disc of this type is shown in Fig. 6. It appears that the angular thickness of the aperture edge at the plane of definition is 171 degrees. This is only 9 degrees less than the maximum available and much more than what is usually used (90 to 135 degrees). The correction required for the small amount of radiation transmitted at the top of the V shaped, circular edge constituting the plane of definition of the diaphragm is considerably reduced by this design.

A modification of the diaphragm in Fig. 6 is depicted in Fig. 7 here a slightly coned surface is used in place of part of the length of the cylindrical hole shown in Fig. 5.

The design using a coned surface in whole or in part, may be expected to give a more accurate position of the plane of definition. The high density of the material used further contributes to the improvement. The diaphragm

Table 2

*Results of ionometric measurements with different diaphragms in Washington 1956*

Diaphragm No	Volt	Exposure time in seconds	Average volt per minute	Calculated relative values of ionization
6a	28.64	200	11.584	0.5636
	28.59			
	28.59			
8a	25.37	100	15.22	Average 15.23 = 1.000
	25.38			
	25.36			
8a	25.40	100	15.24	
	25.38			
	25.42			
10a	23.81	60	23.78	1.5614
	23.75			
	23.79			

Table 3

*Diaphragm diameters obtained from direct and ionometric measurements in Washington 1956 and from direct measurements in Stockholm 1959*

Diaphragm No	Calculated from the relative values in Table 2 and the rear 8a value given in column 3 of Table 1	Measured in Stockholm in 1959	Difference ( % )
6a	6.003	6.001	0.03
8a	7.997	7.995	0.03
10a	9.993	9.996	0.03

discs in Figs 5, 6 and 7 may be used alternatively, and a direct comparison is thus very easy.

Our measurements in 1946 of diaphragm 8a, of the type shown in Fig. 4 were made crosswise in two perpendicular directions at the front surface, a cylindrical hole being assumed from the method of machining. In 1956 this diaphragm was separately measured with very high precision at the NBS and in 1959 was re-measured at our institute by a measuring device more accurate than that used in 1946. All the results obtained with this diaphragm are collected in Table 1.

The NBS results show that the hole is slightly coned with a calculated front-rear average of  $7.9910 \pm 0.04$  per cent. This value is very nearly the same as that measured at the middle. Our own values in the last column give a similar result. The average is 7.9933 which is only 0.01 per cent different from the just-mentioned average of the NBS values.

Fig. 4 shows that the rear diameter is that normally defining the cross-section of the beam. If we thus compare our latest rear value 7.9915 with that obtained at the NBS 7.99719 it appears that the difference is about 0.03 per cent.

Table 4

*Measurement results obtained with each of the seven separate parts of the divided collector electrode*

Collector electrode No	Length of collector electrode in cm	165 kV	165 kV
		HVL = 0.055 mm Cu V in volt per minute	HVL = 0.35 mm Cu V in volt per minute
1	5.00	11.21	11.54
2	5.00	11.20	11.58
3	5.00	11.15	11.53
4	5.00	11.05	11.50
5	5.00	10.86	11.54
6	5.00	10.84	11.52
7	5.00	10.85	11.50

As already mentioned, diaphragms of the type shown in Fig 4 were used as the intermediary medium in the comparison. These diaphragms were ionometrically compared at the NBS free air standard chamber. The results obtained are collected in Table 2.

Diaphragms 6a and 10a have been re-measured in our institute in the same way as shown above for diaphragm 8a. The measurement results and the results calculated from the direct and relative measurements in Washington, all of them to three decimals, are given in Table 3. It appears that the difference is within  $\pm 0.03$  per cent.

According to RAJEWSKY et coll (ref 3) it is usually possible to attain an accuracy of  $\pm 0.003$  mm in the measurement of the aperture diameter. If the diameter is of the order of 10 mm, the accuracy will be  $\pm 0.03$  per cent. The differences in Table 3 agree with this.

An error of  $\pm 0.3$  per cent is estimated in the last ICRU report (ref 1) in the determination of the measuring air volume. The diameter error found above is only one tenth of that volume error. As the maximum error that may occur in free air standard chamber measurements is  $\pm 1.1$  per cent (ref 1), further efforts to reduce the error in the determination of the diaphragm diameter will not appreciably influence the total accuracy.

Two diaphragm discs have been produced to fit the new type of diaphragm holder shown in Fig 5: one of the type designated 3 in Fig 5 and one of the type shown in Fig 6. The first mentioned has a cylindrical hole 10.0165 mm in diameter and the other an aperture diameter of 10.0075 at the plane of definition.

It is a common experience that a free air standard chamber equipment is mainly used for calibration of radiation measuring instruments provided with cavity ionization chambers or other detectors. When such an instrument is to be calibrated in this laboratory, its detector is arranged in the following way (ref 7). The detector is inserted into the beam through a special opening

Table 5

*Symmetrical addition of the experimental results in Table 4*

Collector electrode No	l = total length of collector electrode in cm	165 kV		165 kV	
		HVL = 0.055 Cu		HVL = 0.35 Cu	
		Sum of v	v/l	Sum of v	v/l
4	5.00	11.05	2.210	11.50	2.300
3+4+5	15.00	33.06	2.203	34.57	2.303
2+3+4+5+6	25.00	55.10	2.203	57.67	2.307
1+2+3+4+5+6+7	35.00	77.16	2.203	80.71	2.306
Average v/l		= 2.203		= 2.304	
		± 0.16%		± 0.15%	

in the cylindrical high tension electrode of the free air chamber, with its longitudinal centre line at the same focal distance as the centre of the collector electrode and passing through and lying perpendicular to the centre line of the beam. By this experimental arrangement the readings of the instrument may be compared with those of the free air standard chamber without correction for differences in beam attenuation in air and without changing the position of the standard chamber. If the instrument is later used with different lengths of its detector stem exposed to radiation, the corresponding correction for the variation in response with the stem length irradiated has to be applied. A separate investigation of this variation is a necessary part of the test program to which for example cavity chambers have to be subjected before final calibration.

The writer as early as 1930 in the first investigation of the free air standard chamber of this institute used a collector electrode divided into seven equal parts each of which was arranged to be independent of the others (ref. 4). The quantity of electricity collected by each of these seven collectors could thus be measured separately. The roentgen tube used was a Metwax Metalix having a thin glass window. According to a separate investigation (ref. 6) the glass window thickness of this tube was 0.33 mm which was found to be equivalent to 0.27 mm of aluminium. With a tube voltage of 165 kV constant potential and no added filter, the HVL of the beam measured by the standard chamber was 0.055 mm Cu. By an added copper filter the HVL was increased to 0.35 mm Cu. Using these two beams measurements of the ionization were made separately by each of the seven collectors. The results obtained are given in Table 4. The change in potential between the plates of the collecting precision capacitor,  $v$ , is given in volt per minute. The values in column 3 refer, however, to the capacitance of the collecting capacitor other than those in column 1. It is seen that  $v$  obtained with no added filter, is slightly reduced by absorption in the air along the collector electrodes. This effect disappears with the added copper filter.

If the  $\nu$  values in Table 4 are symmetrically added, and each sum divided by the corresponding collector length, we obtain the result shown in Table 5. It appears that  $\nu/l$  is of good constancy at both the beams. This verifies that it is correct to refer the measurement result to the centre of the collector electrode.

### Acknowledgement

The measurement results obtained at the U.S. National Bureau of Standards, Washington and communicated in this paper are published with due permission. The author wishes to express his sincere thanks to H. O. WYCKOFF who made the facilities of the Bureau available and personally devoted considerable time to the measurements.

### SUMMARY

Improvements of the Swedish roentgen standard laboratory equipment introduced in connection with an increase of its calibration capacity from 200 to 300 kV are described. The employment of a sub-divided collector electrode as well as the characteristics of the new 300 kV tube and the new diaphragm system and precision measurements of diaphragms are discussed.

### ZUSAMMENFASSUNG

Ein Ausbau der Kalibrierungsmöglichkeiten des schwedischen Röntgenstandardlaboratoriums von 200 kV auf 300 kV wird beschrieben. Die schon früher verwendete 7 teilige Messelektrode in der Standardkammer, die Eigenschaften der neuen 300 kV Röntgenröhre und des neuen Blendensystems, nebst Präzisionsmessungen einzelner Blenden werden ausführlich erörtert.

### RÉSUMÉ

Description de perfectionnements apportés à l'équipement du laboratoire suédois des étalons roentgen en même temps que sa capacité d'étalonnage passe de 200 à 300 kV. L'auteur étudie l'emploi d'une électrode collectrice subdivisée ainsi que les caractéristiques du nouveau tube de 300 kV, le nouveau système de diaphragme et les mesures de précision des diaphragmes.

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# REPORT ON MEETING ON PRACTICAL METHODS OF ASSISTING RADIOTHERAPY CENTERS IN LESS DEVELOPED AREAS

International Atomic Energy Agency/World Health Organization

Montreal, Canada, September 4—6, 1962

In 1959 and 1962 the International Atomic Energy Agency and the World Health Organization jointly convened two meetings of experts in radiotherapy and radiation physics. The first meeting was held in Vienna from 3—5 August 1959, the second in Montreal from 4—6 September 1962. Although the two meetings took place under different titles and with different participants, they were both concerned with the development, organization and practice of radiotherapy, with particular reference to high energy radiation. The Chairman of both meetings was Professor Sir Brian Windever.

It was the intention of the 1959 Vienna meeting to produce basic recommendations which would be of value to all authorities responsible for radiotherapy in cancer treatment, to those considering the establishment of radiotherapy centers, and to practicing radiotherapists and radiation physicists. The recommendations of the meeting were drawn up with a view to giving practical guidance rather than as a contribution to fundamental knowledge on the subject.

The recommendations of the 1959 meeting were published in various languages in a number of radiological journals and also in booklet form together with some background information, under the title *Use of Radioisotopes and Supervoltage Radiation in Radiotherapy: Present Status and Recommendations* (International Atomic Energy Agency, Vienna, 1960). Copies of the booklet are still available in English, French, Russian and Spanish.

The 1962 Montreal meeting was conceived as a follow up meeting in which the subject matter of the earlier meeting would be reconsidered with particular reference to the problems of developing countries. Some of the topics which were mentioned only briefly in the first meeting were therefore dealt with in more detail, together with other topics of special interest to developing countries.



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## REPORT

### I Terms of reference

The deliberations of the working party were directed towards assisting developing countries in the application of radiation sources in cancer therapy

### II Introduction

It is desirable for a nation considering the establishment of radiotherapy centers to evaluate the overall needs of its people and to arrive at a decision as to the necessity for increasing its effort against cancer. There is no doubt that radiation therapy is and may well remain an essential element in the medical effort to treat cancer patients and if a proper organization for the treatment of cancer is developed an efficient radiotherapy service is therefore essential.

The recommendations made by this working party are based on the Report of the Study Group on the Use of Radioisotope Teletherapy Units and Supervoltage Radiation in Radiotherapy 1959 (Use of Radioisotopes and Supervoltage Radiation in Radioteletherapy Present Status and Recommendations IAEA Vienna 1960). The working party accepted

the organization detailed in the 1959 Report Parts I, II and III as the basic minimum for an efficient radiotherapy service but considered that the following changes in emphasis are appropriate in the light of further experience with supervoltage therapy

(a) Caesium 137 or any other radioisotope emitting radiation of energy less than 1 MeV should not be regarded as a form of supervoltage. Suitably designed caesium 137 units can however be used as substitute for orthovoltage X-ray machines

(b) Greater emphasis should be placed on the need for physics services. In addition to trained physicists who should be employed full time in radiotherapy, attention should be drawn to the necessity for the provision of adequate physics laboratories and equipment

(c) Attention is drawn to the desirability of having relatively uncomplicated machinery for routine treatment where there are difficulties in adequate maintenance

### III The establishment of radiotherapy centers

A radiotherapy center should provide acceptable medical and scientific conditions for the treatment of cancer patients by means of radiation. This can be done only if the center is related to the medical and scientific community as a whole because while radiotherapy is an essential medical element in the treatment of cancer it is not the sole means for so doing. Co-operation with other medical specialities is therefore necessary. Similarly, continuing contact with the scientific community will ensure that appropriate scientific developments will be applied to the patients

In order to provide the necessary conditions for the practice of radiotherapy, the radiotherapy service should be set up in close association with other clinical departments and also with the basic medical sciences. It is therefore desirable that a radiotherapy center be placed within a medical teaching institute

The working party considers it important that a radiotherapy center should accept its responsibilities in the training of personnel at both undergraduate and postgraduate level. Professional staff, both medical and non medical, should undertake the teaching and training of radiotherapy personnel. Furthermore, some instruction in radiotherapy should be given to all medical students so that they can be provided with an overall picture of cancer treatment. Such instruction would also encourage subsequent recruitment of radiotherapy trainees

A radiotherapy center should also provide facilities for research and development work and professional staff, both medical and non medical, should be allowed and encouraged to participate in such research

The radiotherapy center must be in the charge of a radiotherapist. The physical conditions of treatment with ionizing radiations are complex and their accurate planning and realization are essential for the patient if his cancer is to be controlled with minimal likelihood of damage to normal tissues and if the staff and public are to be guarded against overexposure to radiation. The radiotherapist must therefore be assisted by a physicist responsible to him for all statements relating to the absorption of ionizing energy in the patient, staff and the environment

The professional staff must furthermore be supported by technical staff such as radiotherapy and physics technicians, so that they may effectively discharge their responsibilities. In addition, it is important that an engineer or technician capable of maintaining and servicing apparatus and equipment be available at all times

### IV Responsibilities and duties of radiotherapy personnel

#### *A—Radiotherapist*

Since the most important part of a radiotherapist's work concerns the treatment of malignant diseases, the following details refer specifically to his duties with respect to this type of disease.

**1 Clinical duties** The radiotherapist collaborates with his clinical colleagues in diagnosing the disease and in making the fundamental decision as to whether or not it should be treated by radiotherapy. He is responsible for the medical care of the patient undergoing radiotherapy. He is also responsible for ensuring that adequate records of the patient and his treatment are kept.

**2 Treatment planning** The aim of treatment planning in radiotherapy is to irradiate a defined volume of tissue and to deliver to it a dose considered as optimum. The radiotherapist is responsible for this task; he is helped by physicists and technicians but his responsibility remains complete. His minimum duties in treatment planning are the following:

(a) Localization of tumour, delineation of the target volume, determination of the relation of the target volume to the external contour of the body in the treatment position and neighbouring structures.

(b) Choice of the type of radiotherapy, e.g. external beam therapy or interstitial therapy.

(c) Deciding the dose: total absorbed dose in the tumour, fractionation, overall time and number of sessions.

In some cases his work for treatment planning can be limited to these items. Usually, however, in conjunction with the physicist, he also chooses the best way of delivering radiation to the patient.

After estimation of the absorbed dose within the body of the patient by the physicist, he must satisfy himself as to the dose received by the radiosensitive tissues in order to be sure that none of them receive a dangerous dose.

**3 Conducting the treatment** (a) Clinical examination of the patient at least twice weekly in order to judge the effects of the radiation. (b) Overall verification of the technician's work, especially as regards the positioning of patients before irradiation and the absence of any change of position during treatment.

**4 Follow up of the patient after treatment**

**5 Radiation protection** The senior radiotherapist is responsible for protection of his staff against radiation.

**6 Teaching and Research** As already indicated, an important part of the radiotherapist's work may lie in the fields of teaching and research.

### *B—Physicist*

Generally speaking, the responsibilities of the physicist fall into three categories: services related to the treatment of patients, teaching and research. The amount of time he will spend on each of these will depend on the state of development of the radiotherapy department and the hospital with which he is associated.

As minimum duties, the physicist shall be responsible to the radiotherapist for:

- 1 All aspects of radiation dosimetry
- 2 Collaboration in treatment planning
- 3 All physical aspects of radiation protection
- 4 All physical aspects of the use of radioisotopes
- 5 Design and construction of ancillary apparatus, such as beam directing devices
- 6 Overall supervision of maintenance of equipment
- 7 Advice on the choice of new radiotherapy and radioisotope equipment and building design problems

### *C—Radiotherapy technician*

In general the duties of the radiotherapy technician are to assist the radiotherapist to plan and execute the treatment of the patients and to record relevant information concerning the treatment. The radiotherapy technician is directly responsible to the radiotherapist for these duties which may include:

1. Assisting the radiotherapist in the day to-day treatment of the patient including positioning the patient for treatment, verification throughout the irradiation that the desired position is maintained and otherwise assisting the radiotherapist as required in the care of the patient.
2. Preparing equipment for daily use, for example warming up X-ray machines, calibrating treatment units (under the general direction of the physicist) and recording the value obtained.
3. Using beam directing aids including field localizing films.
4. Assisting the radiotherapist in the preparation and use of positioning aids such as body cast moulds, etc.
5. Maintaining records of the factors of treatment. These will include statements of exposure, dose, treatment time, relevant calculations, etc.
6. Assisting the radiotherapist in the therapeutic use of sealed and unsealed radioisotopes.

## **V Working conditions**

As already emphasized, radiotherapy should be carried out within the general framework of medical and surgical services and should be closely integrated with other branches of medicine. The aim should be to develop a system whereby the radiotherapist is a competent clinician who is a full partner in the team work necessary for the treatment of cancer. He should be sufficiently trained and of such caliber as to have clinical control of patients and be able to have hospital beds under his own control.

In view of the variety and technical nature of the tasks which the radiotherapist must perform and the grave handicap which a dispersion of his activities among various occupations presents both for him and his center, it is desirable that as far as possible he should devote his full time to radiotherapy in a single place of work. To this end adequate remuneration must be provided. In this way will it be possible to gain the maximum value from the personnel and equipment of a radiotherapy center.

The physicist must be recognized as a full working partner with the radiotherapist. He must be given facilities which will allow him not only to meet the day to-day clinical needs of the department but also to make fundamental contributions to the treatment of cancer by radiation. To this end he must have:

- (a) Adequate laboratory space and instrumentation
- (b) Machine shop facilities
- (c) Competent technical assistance as the development of the department merits
- (d) Opportunity for research

In order to attract a man of suitably high caliber, the salary and career prospects must be commensurate with those obtained in comparable scientific positions.

Adequate library facilities and the opportunity to attend meetings are also essential to all personnel.

## **VI Training and assistance**

Training of staff is one of the greatest problems in the building up of radiotherapy services. The following lines of approach are considered to be important:

### *A—Fellowships*

It is recognized that effective operation of a fellowship programme is one of the best means of achieving improvement in radiation therapy. It is urged that the number of fellowships in radiotherapy and radiation physics be increased and their existence made known on a wide scale. The working party agreed that the operation of the fellowship programme should be integrated with the overall planning leading to the establishment or development of a center for radiation therapy.

The fellowship programme should include opportunities for training for persons with no prior experience in radiotherapy or radiation physics as well as arrangements for shorter periods of time for persons whose qualifications may range up to and include full competence in their field and who wish to obtain experience in a special facet. A training grant may be necessary for a few months only or may be required for a three year period in the case of a person who needs full training.

As noted in the 1959 report, the larger teaching centers in all countries should recognize an obligation to assist the sponsoring organizations to train individuals in this field.

In the course of the discussion of the working party on fellowship training, a number of practical points emerged. Although these matters are already known to the IAEA and WHO, it was considered worthwhile to bring them forward again for the sake of emphasis.

1 *Language barriers* It is necessary that a Fellow who is to receive all or most of his radiotherapy training have a good working knowledge of the language of the country to which he is assigned. If this condition is not satisfied, the value of the training is reduced. This is particularly true for medically qualified Fellows, since ability to communicate easily and accurately with patients is essential to their training.

2 *Early communication between trainee and training center* It is suggested that in all cases the trainee be urged to write to the prospective training center at as early a date as possible and that the training center should communicate with him. This would allow an interchange of ideas about his desires and needs and permit the center to recommend reading material. Much time could thus be saved both by better definition of his training programme and by prior acquisition of basic knowledge. The early contacts will facilitate the definition not only of the programme but also of the length of the fellowship.

3 *Level of knowledge* It is unfortunately true that the level of knowledge presumed by the sponsoring organization and by the training center is not in fact always met by the trainee. As mentioned above, early communication between the trainee and the institution responsible for the training would do much to clarify this point. In some instances it may be necessary to revise the proposed programme in such a way as to render it appropriate to the candidate's actual level of knowledge. The decision should rest with the training director who may also recommend, if necessary, that the period of training be extended.

4 *Assurance of a position after completion of training* It is recognized that this is a difficult problem. Many training centers have had the unhappy experience of training excellent Fellows who, upon return to their home countries, have found no suitable positions. This problem is such a serious one both for the Fellow and for the training institution that it is felt that fellowships in radiotherapy should not be granted unless a suitable post is assured for the returning Fellow.

The sponsoring organizations should therefore seek by all appropriate means assurance that the interested governments understand the gravity of this problem and the need for making every effort to ensure suitable working conditions for the trainee on his return, which may include the provision of certain necessary items of equipment.

5 *Timing of fellowships* Many centers which accept Fellows have organized training programmes which begin at a certain period of the year. It is urged that in such cases fellowships should be timed so as to fit in with these programmes. Otherwise months may be wasted and the value of the fellowship considerably reduced.

6 *Selection of Fellows* The number of candidates for fellowships in radiotherapy and radiation physics may well exceed the number of available fellowships. It is clearly desirable to assure the greatest efficiency in the fellowship programme and it is therefore desirable that great care should be given to ensuring a wide geographical distribution of the candidates and to the difficult task of selecting the best recipients both on a national and international basis.

#### *B—Visiting experts*

These represent a very important form of assistance and must be encouraged. They must be integrated in a more general programme of international aid. Advanced countries and institutes should be urged to provide facilities for their staff to participate in such programmes.

There are two main categories of visiting experts. Long visits, i.e. of several months, will enable a broad new field of work to be initiated; short visits of experts will point to the direction in which a special effort is needed and will help the experts themselves to understand the problems of the centers visited and to guide the work of those who may subsequently receive fellowships.

#### *C—Co-operation and exchange of personnel between institutes*

Schemes of co-operation between individual institutes, either within a given country or in different countries, appear to be a particularly good way of providing training facilities on the one hand and unusual scientific or clinical material on the other. The working party draws attention to the possibility of the sponsoring organizations acting as intermediaries in arranging such co-operation. It is expected that the arrangements will include the exchange of professional and technical personnel between the two centers. It is suggested that such exchange should be arranged either as a follow up to the visit of an expert from one center to the other or in the course of a programme of co-operation between the two centers.

#### *D—Training courses*

The working party recognized that a formal training course of some weeks or months duration and organized on a national, regional or international basis can be of value provided it is realized that a short course cannot replace the more lengthy training in a radiotherapy institute which is required to produce qualified radiotherapists and radiation physicists. Short courses may however perform a useful function in giving advanced training in certain fields to already qualified personnel.

#### *E—Regional advisers*

The working party agreed that the appointment of radiotherapists and radiation physicists as regional advisers would be valuable in many regions of the world. These advisers should be appointed on a long term basis for the purpose of helping and advising all the radiotherapy centers within a defined geographical region. Such personnel should be carefully chosen, having regard to their technical and personal qualities.

#### *F—Regional symposia*

The working party considered that the holding of regional symposia should be encouraged. Such symposia on both medical and physical aspects of radiotherapy would be of benefit to all personnel in less-developed regions of the world and would foster co-operation in these areas.

## BOOK REVIEW

**DIE INTERNE KREBSTHERAPIE** Von H. D. Diamond Deutsche Übersetzung von H. Obrecht und P. Berg 158 Seiten 42 Abbildungen und 23 Tabellen Georg Thieme Stuttgart 1960 Price DM 29 50

It is becoming increasingly necessary for clinicians to have access to an informative review of the chemical agents available for the treatment of malignant disease. Thousands of new substances are tested each year for their carcinoid effect although only a few are submitted for clinical trial and even fewer gain clinical use. It is widely accepted that malignant disease cannot be cured by chemical agents but this does not necessarily mean that the course cannot be influenced by medication. Clinically useful chemotherapeutic agents and hormones are already available in such large numbers that much confusion and uncertainty exist regarding their fields of application and dosage. Insufficient knowledge concerning these substances results in their not being so widely used as they should be in the palliative treatment of neoplasms.

Thieme's Publishing House has issued *Die interne Krebstherapie* a German translation of the original work *The Medical Management of Cancer* published in America in 1958 and written by H. DIAMOND who has had wide experience in this field. The book deals with a number of malignant diseases — one chapter for each — that have often proved to respond to chemotherapeutic and hormonal methods of treatment. Malignant lymphomas and leukemias are afforded pride of place but other types of malignancy such as mammary and pulmonary carcinoma are also included. Attention is mainly concentrated on chemotherapy and hormonal treatment while intracavitary radiologic treatment is mentioned only for information. Intracavitary radioisotope therapy is however given a special exhaustive chapter by two radiotherapists.

This readable book contains interesting information not only on the treatment of different diseases but also on their symptomatology and variations. No objections can be raised to the methods of treatment described although other forms might in certain cases prove equally satisfactory. The procedures are competently and simply described usually with reference to original publications. The work is somewhat biased as the author refers almost exclusively to experiences reported in the Anglo-Saxon literature; this has been rectified to some extent by the publishers who have added a list of German publications to the references given for each chapter. The brief descriptions of radiologic treatment methods are largely in accordance with the methods and doses used in Sweden.

The book should be of interest to all clinicians who deal with cases of malignant disease. Despite its age it is still of great value in practice seeing that many years of clinical trials are necessary before a new preparation can be put on the market for general use. A few substances fairly generally employed in recent years (e.g. cyclophosphamide-endoxan and phenylalanine mustard — Melfalan, Sartolysin, PAM) are however missing. Nor is there any mention of more recent forms of administration such as perfusion and continuous intra-arterial infusion although admittedly these are methods that are not yet ripe for general clinical use.

Bo Johansson

## VERSATILE POSITIONING AID IN FIXED AND MOVING FIELD THERAPY IN HEAD AND NECK TUMORS

by

RUIHRI PEREZ TAMAYO and CHARLES E. SEIBERT

In this progressive era of rapid medical advancement and development of more precise treatment techniques it is remarkable that so little attention has been given in the literature to the importance of immobilization of the head and neck for radiotherapy of tumors of these areas (see list of references). The necessity for immobilization may be obvious yet publications concerning how to achieve this point are very rare indeed. In no other part of the human body is immobilization so critically vital. The extreme radiosensitivity of the uninvolved eye is only one of the many self evident examples of the crucial need for complete immobilization while treating the head. Fortunately this is one part of the human body where motionlessness can be obtained very effectively. Thus the radiotherapist should provide precise means to hold the head and neck of the patient.

Not only children but comatose unconscious disoriented or uncooperative patients need to be treated while properly restrained. The treatment of the most cooperative patient can be unsatisfactory due to insensible involuntary movement since the final dose distribution depends on the position of the field and the position of the field depends on the position of the part of the body under treatment.

From the Department of Radiology Division of Radiotherapy (Director Prof R. Perez Tamayo) University of Colorado Medical Center Denver 20 USA. Submitted for publication 12 November 1962.



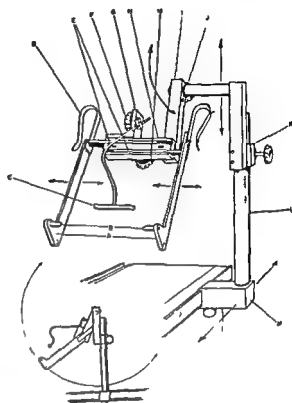


Fig. 1

- A — Far support arms
- B — Ear pieces
- C — Vertical extension stabilizer bar
- D — Cassette clip
- E — Lateral adjusting racks
- F — Stabilizing clamping bracket knob
- G — Stabilizing clamping bracket
- H — Lateral adjustment rack housing
- I — Rack pinion adjusting knob
- J — Swivel yoke
- K — Swivel yoke locking knob
- L — Elevating pinion
- M — Calibrated upright
- N — Table clamp

Immobilization therefore, is also important because it is intimately related to accurate field placement. Over and above the inherent limitation of the ability to recognize the exact localization and extent of certain lesions, the head and neck lends itself to many informative examinations and better localizations. Ventriculograms, pneumoencephalograms, arteriograms and other special procedures are good examples of the vast diagnostic aids available to the radiotherapist when in search of guiding points for the field placement in the treatment of brain lesions. Indirect laryngoscopy, soft tissue technique roentgenograms of the neck and tomograms are good examples of diagnostic procedures which are valuable in the localization of the lesions of the neck.

Once the reasonable localization of a lesion has been accomplished, treatment fields can be oriented accordingly and related to reference points. The unchangeable orbitomeatal base line may be used as a constant reference (cf. Fig. 2). This line maintains its relative position in the head in any degree of flexion of the neck and permits treatment reproducibility. The correct initial field adjustment can be checked with placement films and the entire procedure may be repeated daily, without error if the known position of the fields relative to the base line and the known position of the source relative to that of the



Fig 2 Patient and head holder in position of horizontal line drawn in black



Fig 3 Patient (lying horizontal) and head holder in position for treatment of neck let on

head or neck are kept constant. Unless this is done, localization and placement are useless.

In the Division of Radiotherapy at the University of Colorado Medical Center, the localization and routine placement films of the fields as well as the immobilization of the head and neck are accomplished with a specially designed positioning aid or head holder.

Allowing for the need and desirability of such a positioning aid or head holder, certain features are then necessary for optimum function and performance.

- 1 The unit must be adaptable for the treatment of either head or neck lesions, yet not be in the path of the primary treatment beam, because then in the primary treatment beam, the skin sparing effect of high energy radiations will be lost and the intensity of medium voltage range will be seriously reduced.

- 2 It must be portable but sturdy. Portability is an important feature in that an unwieldy, heavy immobilizer might find itself more frequently in a storage area than readily available in the treatment room. Durability and strength are, however, necessary features.

- 3 It should be accurate but simple in design and operation to assure speed in the daily treatment of patients.

- 4 It should have provisions to facilitate film localisations.



Fig 4 Example of setting with film cassette in position for localization film

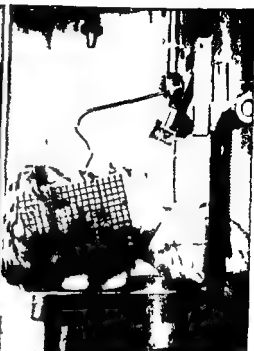


Fig 5 Metallic grid fitting in head holder at alignment of grid line with orbiton collimator line

5 Finally it should afford daily accurate reproducibility of treatment fields by either physician or technician

Following the basic principles of the device used by Dr Isidore Lampe at the University of Michigan, a unit was designed with added features to fulfill the particular needs of the treatment center at the University of Colorado Medical Center. The head holder designed and built for our division of radiotherapy, is depicted in Fig 1.

Functionally, it can be divided into five parts:

1 The calibrated upright part (I) with elevation rack fastened to the treatment table by a table clamp (M). This can be easily moved along the table and will meet the head at variable distances. It is equipped with a scale which designates the position. For treatment of head lesions this upright part is used as depicted in Fig 2 and for treatment of neck lesions it is placed as depicted in Fig 3. The unit, however, can be fastened on the right or left side in either case. Note that the head holder will not be in the way of the source housing while moving therapy is employed thus avoiding possible collision. When not in use, the upright part and the head holder are conveniently stored on a similar clamp on an adjacent wall or table.

2 The elevating pinion (K) fits on the calibrated upright and by turning the

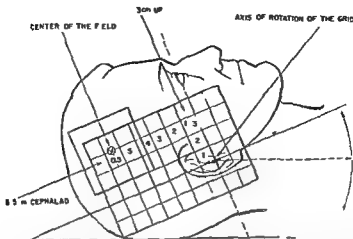


Fig 6 Example of setting of field using grid co-ordinates. The selected center of a treatment field is 3 cm up and 5.5 cm cephalad from the zero point. (These figures are derived from localization field film.) These distances are counted off on the grid and the central beam and cross hairs are moved to coincide with this point. Field size is then limited to the desired dimensions.

elevating pinion knob the pinion can be elevated or lowered to any desired height.

3 The swivel yoke (I) is attached to the elevating pinion and is free to pivot in a rotary fashion as shown in Fig. 1. It is locked into any desired position by the swivel locking knob (J). The lateral adjustment rack housing (H) is attached to the swivel yoke. The housing contains lateral adjusting racks (E) which are moved inward or outward by the rack pinion adjusting knob (H'). Ear support arms are attached to the adjustment rack and ear pieces (B) are attached to these.

4 A flexion extension stabilizer clamping bracket (B) and stabilizer clamping bracket knob (F) hold the vertical extension stabilizer bar (C).

5 Accessory features include cassette clips (D) for cassette holding which are attached to plastic ear support arms, holes present in the ear pieces to permit accurate placement into the auditory canals, and a plastic grid with metal cross hatch grid which will fit into the ear holder pieces (see Fig. 4).

The use of the head holder is best described by one example: the positioning of a patient for the treatment of a brain tumor. The patient assumes a comfortable supine position on the treatment table. Any comfortable flexion or extension of the neck can be used for the treatment of brain tumors because the final setting is based on the orbitomeatal line, and this reference remains the same with flexion or extension of the neck. This feature of the head holder is especially

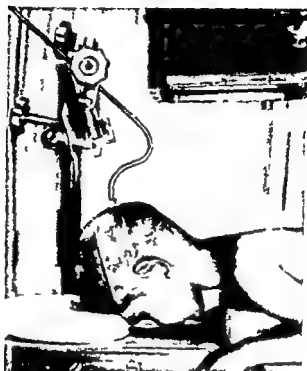


Fig. 7 Example of use of head holder in treatment of posterior field in child with medulloblastoma.

rewarding in short necked patients or those with arthritic changes which would limit their ability to assume a forced position. The general position is that of the patient shown in Fig. 2. The elevating pinion is lowered or elevated until the plastic ear pieces are at the level of the auditory canal. Combined adjustments of the elevating pinion and the pivoting movement of the swivel yoke facilitate this preliminary step. The ear support arms are approximated by turning the rack pinion adjustment knob until the ear pieces fit into the auditory canals and the head is held snugly. The pressure maintained by the ear pieces and supporting arms need not be great. Indeed, it was quite surprising to observe the small amount of pressure needed to stabilize semicomatose patients and potentially uncooperative pediatric cases. The mere sensation of the ear pieces in place, while not uncomfortable, seems to promote immobilization. The flexion-extension stabilizer bar is then adjusted to one of a number of selected sites to maintain a given degree of neck extension. Examples of selected sites might be the forehead, the bridge of the nose, the anterior nasal spine or the chin. Here, again, pressure is not demanding but only a gentle reminder for the patient not to move. The fields can then be adjusted. The position of the upright part, the height of the elevating pinions and the angle of the swivel

yoke are calibrated and may be charted so as to duplicate the entire setting daily

For accurate daily fields, portal placement, one needs an unchanging base line point. It was mentioned earlier that an excellent built in base line is available in the head, i.e. the orbitomeatal line as depicted on Fig. 2. Since this line is unchanged by a degree of flexion of the head or neck, daily accurate field portal reproducibility can be achieved by locating the center of a given treatment field at a perpendicular distance from this line. To accomplish this a plastic grid with opaque grid lines is placed on the ear support arm and rotated until the central grid line coincides with the orbitomeatal line (Fig. 5). The intersection of the cross hairs of the light localizer of the source is made to coincide with the meatus of the ear. Then the collimator is rotated until the cross hairs are superimposed over the orbitomeatal line and the central grid line as in Fig. 6. This constitutes the zero position. A roentgenogram is obtained making use of the treatment source with the head or neck in the treatment setting and the center of the field can then be determined on the film. Its position and size can be noted by taking co-ordinates on the grid from the zero point. (The localization film technique is fully described in another publication.) Using the co-ordinates from the zero point, the central beam is then moved to the selected central field position. Once more the grid and the cross hairs permit the easy placement and alignment of the center of the beam onto the predetermined center point of the field. The superimposition of the cross hairs and grid is simple.

As shown in Figs. 3 and 6 the head holder is easily adapted for lateral anterior or posterior neck portals, with the patient prone or supine. In these areas the vertical extension flexion stabilizer is again of prime importance. Since in the treatment of anterior neck lesions elevation of the chin is imperative to thrust the soft tissue structures of the neck as far anteriorly as possible this feature is again important. As depicted in Fig. 3 full extension can be insured and a neck field can be constructed and adjusted without compromising the cervical cord.

Needless to say, the accuracy required for moving field therapy is easily accomplished with this unit.

### Acknowledgements

This work was supported in part by a Bent County Cancer Fund grant and grant CRT 5084 from the National Cancer Institute, National Institutes of Health.

The assistance of Mr. Richard Raper, mechanical engineer, is gratefully acknowledged.

### SUMMARY

The need and features of a head stabilizing aid for treatment of head and neck tumors is discussed. A lightweight versatile head holder designed to fulfill the needs of immobilization, film localization and accurate daily field placement is described. A simple method of achieving daily reproducible treatments is presented using the orbitomeatal line as a constant baseline.

## ZUSAMMENFASSUNG

Die Notwendigkeit wie auch das Aussehen eines Kopfstabilisators zur Behandlung von Schadel und Nackentumoren wird besprochen. Ein leichter drehbarer Kopfhalter zur Immobilisierung, Filmplatzierung und exakter Feldaueinstellung wird beschrieben. Es wird eine einfache Methode für taglich wiederholbare Behandlungen gezeigt, wobei die meatus-orbitalis-Linie als Basislinie verwendet wird.

## RÉSUMÉ

Les auteurs examinent l'utilité et les caractéristiques d'un moyen de contention pour le traitement des tumeurs de la tête et du cou. Ils décrivent un craniostat léger maniable construit pour permettre l'immobilisation, la localisation du film et la mise en place quotidienne précise du champ. Ils présentent une méthode simple utilisant la ligne orbito-auriculaire comme ligne de base constante pour obtenir un traitement reproductible quotidien.

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## EFFECT OF BREATHING HIGH PRESSURE OXYGEN UPON TISSUE OXYGEN TENSION IN RAT AND MOUSE TUMOURS

by

D B CATER, E L SCHOENIGER and D A WATKINSON

The tissue oxygen tension is an important factor in the radiosensitivity of tumours (CRABTREE & CRAMER 1933 MOTTRAM 1935, 1936, HOLLICROFT LORENZ & MATHEWS 1952 GRAY CONGER, EBERT, HORNSEY & SCOTT 1953, GRAY 1957). Tissues with an oxygen tension greater than 10 mm Hg are about twice as radiosensitive as tissues with an oxygen tension of less than 0.5 mm Hg (GRAY 1961). Because of the rapid cell division in tumours and the anatomical and physiological abnormalities of the blood vessels (CATER GRIGSON & WATKINSON) zones of necrosis are frequently seen. Adjacent to these necrotic areas there are viable tumour cells living under sufficiently anoxic conditions to be relatively radioresistant (THOMLINSON & CRAY 1955). These cells might need 9 000 r to kill them compared with 4 000 r for well oxygenated cells (WRIGHT 1962). It is believed that such anoxic radioresistant cells are an important cause of the recurrence of tumours after radiotherapy.

Practical attempts to deal with this problem have followed four patterns

- 1 To raise the anoxic zones of the tumour to full radiosensitivity by inhalation of oxygen at atmospheric pressure. HULTBORN & FORSSBERG (1954) studied the effect on tumours of the skin and MITCHELL (1957 (a) (b), 1960) has used oxygen as a radiosensitiser since 1953.

Submitted for publication 11 October 1962



## ZUSAMMENFASSUNG

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## RÉSUMÉ

Les auteurs examinent l'utilité et les caractéristiques d'un moyen de contention pour le traitement des tumeurs de la tête et du cou. Ils décrivent un craniostat léger maniable construit pour permettre l'immobilisation, la localisation du film et la mise en place précise du champ. Ils présentent une méthode simple utilisant la ligne meatus-auriculaire comme ligne de base constante pour obtenir un traitement reproductible quotidien.

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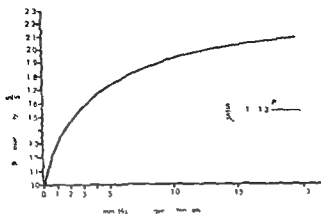


Fig 2 Relationship between rad osensitivity and oxygen tens on the formula of Gray (1961)

### Materials and Methods

The tumours used were spontaneous mammary carcinomas in mice of C3H strain Jensen sarcomas in white Wistar rats and transplantable hepatomas in rats of the August strain. The rat tumours were transplanted into the muscles of the thigh which produced excellent tumours infiltrating muscle and permitted complete immobilisation of the tumour site during the experiment. Tumours transplanted into the subcutaneous tissues of the flank were less satisfactory.

The rats and mice were anaesthetised with urethane 7.5 ml/kg of a 20% w/v solution injected subcutaneously. In the later experiments tracheotomy and carotid cannulation were performed prior to insertion of electrodes. Less than 0.1 ml of heparin (5 000 I.U./ml) was mixed with the saline in a polythene cannula which was tied into the carotid artery. The blood pressure was measured with a Borden type pressure gauge with a 3 cm diameter dial. This was calibrated against a mercury manometer. The dimensions of the oxygen pressure chamber were too small for a mercury manometer to be used.

The animal was fixed to the table A of the pressure chamber (see Fig 1) and the electrodes were inserted and connected to the amplifiers. Measurements of oxygen tension with the animals breathing air were made by the oxygen cathode technique using the apparatus described by CATER, SILVER & WILSON (1959) using rhodium plated stainless steel electrodes described by CATER & SILVER (1961). Recordings were made by the simple device described by CATER, GRIGSON & WATKINSON (1962b). The perspex cylinder (B in Fig 1) was slid into place and the chamber was sealed against an O ring by tightening three winged nuts. Oxygen at atmospheric pressure was administered

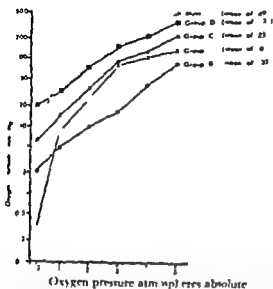


Fig. 3. Log of mean oxygen tension in tumour plotted against the pressure of oxygen inhaled by the animal. Groups according to the initial oxygen tension with animal breathing air: group A 0 to 0.5 mm Hg; group B 0.5 to 4 mm Hg; group C, 4 to 10 mm Hg; group D more than 10 mm Hg.

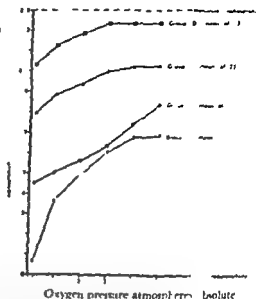


Fig. 4. Mean radioactivity of tumour sites plotted against the pressure of oxygen inhaled by animal. The groups are the same as in Fig. 3 and Tables 1 and 2.

with the chamber closed but with the pressure release valve C open. After 5 minutes this valve was closed and the pressure steadily raised through a reduction valve on the oxygen cylinder. The safety valve D was set to open at 1 atmosphere excess pressure (5 atmospheres absolute). In a typical experiment the following observations were made: the oxygen tension of tumour and muscle, rectal temperature, mean carotid blood pressure, pressure of oxygen in the chamber, and notes on the general condition of the animal. The animal's temperature was controlled by an external heating lamp and by running hot or cold water through the coil of copper tubing F in the lower part of the chamber. In experiments on cerebral oxygen tension the rat's head was held in the stereotaxic instrument, F mounted in the chamber, and the electrode was lowered into the brain to a known depth below the dura by a micrometer screw M through a burr hole in the skull 1 to 3 mm caudally and 1 mm laterally to bregma. At the end of the experiment the rat was killed with chloroform and fixed by injecting 30 to 40 ml of 10% formaldehyde in normal saline into the tail vein or carotid artery. Next day the tumour with the electrodes still in situ was placed in formaldehyde saline for further fixation. The electrodes were removed when the tissues were dehydrated and ready for embedding in wax. Serial sections through the electrode site were made to study the tumour adjacent to the electrode.

Macroscopic and histological examinations of the lungs, liver and kidneys of the animals were also made.

Serotonin (5 hydroxytryptamine creatinine sulphate supplied by Light & Co Ltd) was dissolved in physiological saline and used in a dose of 5 mg of base/kg I.P. Cyproheptadine (1 methyl 4,5 dibenzo [1, c] cycloheptatrienylidene piperidine hydrochloride monohydrate), or Periactin 1 mg/ml was kindly supplied by Dr J. J. F. Merry of Merck, Sharpe and Dohme of Hoddesdon.

## Results

### *Assessment of useful increase of radiosensitivity of tumour with increase of pressure of inhaled oxygen*

The first analysis of the data was made as follows.

The results from the three types of tumour were pooled giving electrodes in 77 different tumour sites for which there was good histological evidence that the tip of the electrode was situated in tumour. These electrode readings were divided into four groups according to their initial value with the animal breathing air. Group A, with an initial oxygen tension below 0.5 mm Hg, group B between 0.5 and 4 mm Hg, group C 4 to 10 mm Hg and group D, above 10 mm Hg. The rationale of this grouping follows from the formula relating oxygen tension to radiosensitivity given by GRAY (1961)

$$\frac{S}{S_N} = 1 + 1.3 \frac{\text{Oxygen tension}}{\text{Oxygen tension} + 4}$$

where  $S$  is the sensitivity at the stated oxygen tension and  $S_N$  is the sensitivity in nitrogen.

A plot of this formula is shown in Fig. 2. An oxygen tension below 0.5 mm Hg is believed to give a radiosensitivity not significantly different from the anoxic radiosensitivity of 1. An oxygen tension of 4 mm Hg gives a sensitivity of 1.65, i.e. half way to maximum radiosensitivity which is taken as 2.3. An oxygen tension of 10 mm Hg gives a radiosensitivity of 1.9. Fig. 3 shows the rise of mean oxygen tension of each group as the pressure of inhaled oxygen was raised from 0.2 to 5 atmospheres absolute. The oxygen tension is plotted on a log scale. The tumour oxygen tension obtained from each electrode at each pressure level of inhaled oxygen expressed in atmospheres was then converted into its equivalent radiosensitivity. A change of radiosensitivity of 0.2 was arbitrarily chosen as a significant increase or decrease for the purpose of scoring and on this basis Table 1 was constructed.

It will be seen from this table that over half the tumour zones investigated showed an oxygen tension of less than 4 mm Hg when the anaesthetised rats and mice were breathing air. When the animals breathed oxygen at atmospheric pressure 16 electrodes showed an increase of radiosensitivity of 0.2 or more and one electrode showed a decrease. On the basis of one plus for every

Table 1

Number of tumour sites in each group which would have an increase of radiosensitivity of 0.2 or more

Group	Initial oxygen tension (mm Hg) breathing air	Initial radiosensitivity	Change of pressure of inhaled oxygen in atmospheres absolute					
			0.2 to 1	1 to 2	2 to 3	3 to 4	4 to 5	0.2 to 5
A	0 to 0.5	100 to 100	26	16	14	06	01	36
B	0.5 to 4	100 to 112	$\frac{6}{32}$	$\frac{4}{32}$	$\frac{3}{32}$	$\frac{7}{32}$	$\frac{1}{32}$	$\frac{23}{32}$
C	4 to 10	112 to 123	$\frac{8}{73}$	$\frac{1}{73}$	$\frac{2}{73}$	$\frac{3}{73}$	$\frac{2}{73}$	$\frac{16}{73}$
D	10 to 40	123 to 138	0.13	0.13	0.13	0.13	0.13	13
Total all groups	0 to 40	100 to 138	$\frac{36}{77}$	$\frac{6}{77}$	$\frac{4}{77}$	$\frac{10}{77}$	$\frac{9}{77}$	$\frac{49}{77}$
Total net scores <sup>1</sup>	0 to 40	100 to 138	26	10	10	15	13	111

<sup>1</sup> A rise of radiosensitivity of 0.2 counts one. A fall of 0.2 counts one.

0.2 increase of radiosensitivity the score was 26 + after subtracting one negative response. The table shows that the change from air to oxygen at 1 atmosphere scores most heavily, but that useful increases of radiosensitivity occur even up to 5 atmospheres absolute. A plot of the mean radiosensitivity indicated by the electrodes in each group at the different pressures of inhaled oxygen is shown in Fig. 1.

Another important consideration is the number of tumour sites which have reached near maximum radiosensitivity at each pressure level of inhaled oxygen.

Table 2

Number of tumour-electrodes showing near maximum radiosensitivity (equivalent to 100% oxygen tension i.e. 40 mm Hg) with the anaesthetised animal breathing oxygen at various pressures

Group	Initial tumour oxygen tension	Pressure of inhaled oxygen in atmospheres absolute						Total number of electrodes
		0.2	1	2	3	4	5	
A	0 to 0.5	0	1	1	2	2	2	6
B	0.5 to 4	0	1	1	3	6	13	30
C	4 to 10	0	2	7	10	13	17	29
D	10 to 40	1	5	7	10	11	13	13
Totals A B C D		1	9	16	25	32	43	77
Percentage		1.3	10.7	20.7	32.5	41.5	58.3	100%

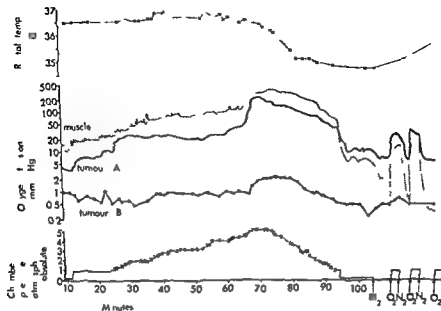


Fig 5 Record of experiment 23 rat with Jensen sarcoma showing oxygen tension plotted on a log scale in two tumour sites A and B and muscle

For this purpose, an oxygen tension of 40 mm Hg was taken. This is equal to the oxygen tension of venous blood when air is breathed and corresponds to a radiosensitivity of 2.18. The data are shown in Table 2 and indicate a steady increase in the number of tumour sites reaching near maximum radiosensitivity as the pressure of inhaled oxygen was raised.

*Relative importance of time under pressure versus height of pressure for obtaining a useful increase of radiosensitivity*

If pressure chambers are to be widely used in radiotherapy, an important practical consideration arises whether a longer time at a lower pressure will be as effective as a short time at a higher pressure. An attempt was made to obtain information on this point and during the first third of this series of experiments the animals were held at each pressure level for the comparatively long period of 5 to 10 minutes. Such an experiment is shown in Fig 5.

The tumour site A, showed a useful increase of oxygen tension when oxygen was inhaled at atmospheric pressure and at two atmospheres absolute near maximum radiosensitivity was reached. The response was quick and no useful increase would have been obtained by the 5 minutes oxygen inhalation at 3 atmospheres absolute pressure.

The tumour, site B, with an initial oxygen tension of 0.5 to 1 mm Hg required the inhalation of oxygen at 5 atmospheres absolute before a useful response



Fig. 6. (A) of electrode B in experiment 23. Fig. 5. Jensen sarcoma with some dilated capillaries and some whorls of loose fibroblast-like cells where tumour cells have degenerated. H and E. 55

was obtained. The inhalation of nitrogen and then oxygen at the end of the experiment gave rapid responses in muscle and tumour at site A, but had little effect on tumour at site B. The site of this latter electrode is shown in Fig. 6. There are many viable tumour cells (Jensen rat sarcoma) near the electrode tip but there are also dilated capillaries and small pale areas where tumour cells have degenerated and been replaced by loose whorls of fibroblast type cells.

Another experiment of this series is shown in Fig. 7 but the tumour is a transplantable hepatoma. The electrode in the tumour (see Fig. 8 for histology) showed a low oxygen tension which increased markedly when oxygen was breathed at two atmospheres absolute. The electrode in connective tissue between the tumour and the muscle showed a high oxygen tension when air was breathed. An interesting finding was the rather slow fall of oxygen tension in the tumour when air breathing was resumed after the inhalation of oxygen at high pressure. This was frequently observed. When these experiments were compared with those in which the pressure was raised more rapidly (rising 1 atmosphere in 2 minutes and remaining 2 minutes at each pressure level, see the first parts of Figs 9 to 13) it is clear that a short period of oxygen inhalation at high pressure was more effective in raising tumour oxygen tension than a long period of oxygen inhalation at low pressure.

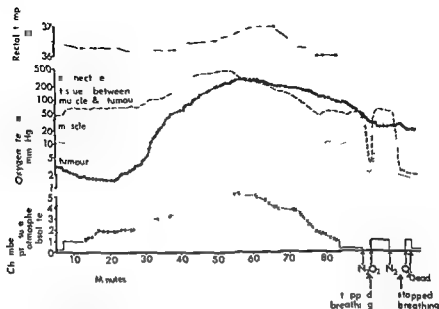


Fig 7 Experiment 24 rat with transplantable hepatoma. Electrode in connective tissue between muscle and tumour — muscle and in tumour — —. The oxygen tension in tumour remains high when breathing after the inhalation of high pressure oxygen.

### *Importance of factors which alter the blood flow through tumour*

1 *Changes of systemic blood pressure* The pressure of inhaled oxygen is only one of the factors upon which tumour oxygen tension depends. Another important factor is the tumour blood flow. CATER et coll (1962b) have shown that tumour oxygen tension is often dependent upon systemic blood pressure and that a fall of systemic blood pressure usually causes a marked fall in tumour oxygen tension. In view of this finding and because it was suspected that inhalation of oxygen under pressure might shock the animals, the systemic blood pressure was measured in the latter half of this series of experiments. However, during the periods of inhalation of oxygen under pressure a considerable increase of mean systemic blood pressure was always observed (see Figs 9, 12, 13, 14). Thus, some of the increase of tumour oxygen tension during oxygen administration under pressure is due to this rise of systemic blood pressure causing an increase of blood flow through the tumour.

2 *Effect of 5-hydroxytryptamine* Because of its action as a radioprotector, CATER et coll (1962b) investigated the action of 5-HT on tumour oxygen tension. They found that 5 mg/kg I.P. caused a more rapid and profound fall of oxygen tension in tumour than in bone marrow, spleen and muscle, and that the rise





Fig. 8. Site of electric lesion in experiment 4 (Fig. 7) hepatoma, moderately good tumor with many small capillaries but some polymorphs present which is least that some degeneration has taken place. H and E  $\times 100$ .

of tumour oxygen tension when oxygen was breathed was usually abolished. Experiments were therefore performed to study the effect on tumour oxygen tension of inhalation of high pressure oxygen following injection of 5 HT.

A typical experiment, in which tumour site A (hepatoma) showed a good rise of oxygen tension during the first period of high pressure oxygen inhalation is shown in Fig. 9. After 5 HT 5 mg/kg I.P. there was no rise of tumour oxygen tension even when oxygen was inhaled at 5 atmospheres absolute. After injection of the anti-5 HT anti-histamine agent cyproheptadine 4 mg/kg I.V., the response of tumour site A, to oxygen inhalation was nearly completely restored. Injection of 5 HT did not diminish the rise of blood pressure due to the inhalation of oxygen under pressure. The oxygen tension in the muscle was diminished by the 5 HT much more in this experiment than in the other experiments of this series.

The experiment 43 in the rat (Fig. 10) and experiment 54 in the mouse (Fig. 11) are more typical in this respect and showed a profound effect of 5 HT on tumour oxygen tension with no effect on the oxygen tension of muscle.

An interesting difference between the oxygen tension in tumour tissue (Jensen sarcoma) which failed to respond to the inhalation of oxygen under pressure after 5 HT and that of the muscle very near to the tumour, in which the response to oxygen inhalation is only slightly reduced by 5 HT is shown in Fig. 10.

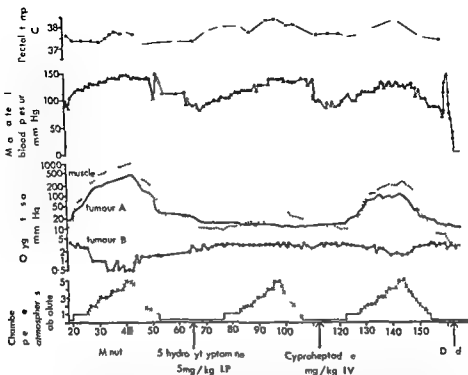


Fig 9 Experiment 37 Rat with hepatoma. From above downwards: rectal temp—■— mean arterial blood pressure —▲—▲—▲— muscle ——— tumour A ——— tumour B ——— and pressure of inhaled oxygen —x— 5-hydroxytryptamine in an amount of 5 mg/kg IP abolished the response of tumour A to oxygen inhalation and cyproheptadine 4 mg/kg IV largely restored the response. Tumour B is an example of an electrode showing a negative response with pressure. 5 HT abolished this and cyproheptadine partially restored the negative response.

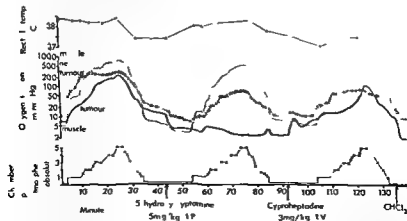


Fig 10 Experiment 43 Rat with Jensen sarcoma. The tumour electrode ——— showed a 5 HT effect similar to tumour A in fig 9 but muscle near tumour x showed only a slight effect and the muscle in the other leg showed no 5 HT effect.

In Fig. 11 is illustrated the 5 HI effect in a spontaneous mammary carcinoma in the mouse but shows the difficulty which was experienced in the mouse in reversing the effect with the anti 5 HI, anti histamine agent cyproheptadine. However after a second dose some response to oxygen inhalation was restored in the tumour. This might be due to 5 HI causing such a marked stasis of blood in the tumour that the anti 5 HI agent cannot easily reach the zones affected.

In Fig. 12 the effect of cyproheptadine given before the 5 HI is illustrated and it will be seen that it partly prevented the 5 HI effect.

3 *Direct pressure effects upon the tumour blood flow* Nine electrodes of the 77 in tumour showed a fall of oxygen tension during the inhalation of high pressure oxygen with the greatest depression usually occurring at the height of the pressure and a recovery of the oxygen tension when the pressure was reduced to atmospheric (see electrode tumour II in Fig. 9). In general histological examination showed such electrodes to be near a zone of necrotic tumour. This unexpected finding with 10 per cent of the electrodes cannot be dismissed as fortuitous. A possible explanation of this rather surprising phenomenon is that necrotic zones of tumour may have cavities containing gas which is not in equilibrium with the blood and may therefore have been compressed when the chamber pressure was raised and caused deformation and vascular stasis in the adjacent area. Examination of Fig. 9 shows that electrode tumour B had this fall of oxygen tension during pressurisation abolished by 5 HI, but that it occurred again, somewhat diminished, after the cyproheptadine. If as is suspected, 5 HI causes vascular stasis and capillary engorgement the behaviour of the electrode, tumour B in Fig. 9, which was also observed in three other experiments would be consistent with the explanation offered.

The possibility of oxygen inhalation under pressure actually reducing the oxygen tension in some zones of the tumour which are already relatively hypoxic has important radiotherapeutic implications.

#### *Synkavit and inhalation of high pressure oxygen*

The effect of the radiosensitizer Synkavit on tumour oxygen tension during inhalation of high pressure oxygen was also investigated. A typical experiment is shown in Fig. 13. Two periods of inhalation of oxygen under increased pressure showed fairly consistent increases of oxygen tension in hepatoma and muscle and a third period after Synkavit 25 mg/kg I.V. indicated less response to the breathing of oxygen under pressure. This was typical of this series of experiments which gave no evidence that Synkavit increased the oxygen response in tumour, a finding consistent with the hypothesis that radiosensitization by Synkavit concerns some other mechanism.

#### *Effect of inhalation of oxygen at high pressures on the oxygen tension of normal tissues*

In most experiments muscle was used as the control tissue, because it was desirable to avoid any procedure likely to shock the animal in view of the

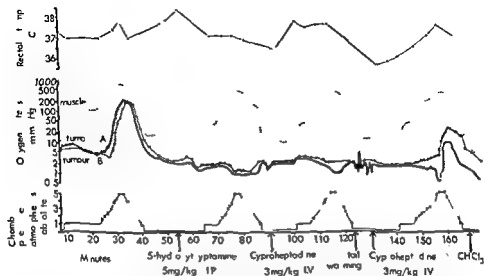


Fig 11 Experiment 54 Spontaneous mammary carcinoma in a C3H mouse. Tumours A and B showed a marked 5 HT effect and two doses of cyproheptadine were needed before the response to oxygen inhalation was partially restored. The response of the muscle was not changed by 5 HT. The temperature changed with oxygen inhalation in spite of active steps to keep the rectal temperature constant.

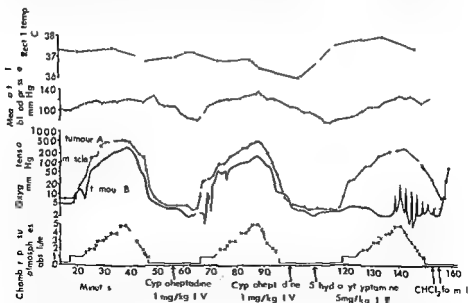


Fig 12 Experiment 51 Rat with 1 patoma. Cyproheptadine did not alter the response to oxygen inhalation but prevented the 5 HT effect on tumour A — and partially prevented on tumour B — — —. The rise of tumour oxygen tension after death is due to intra carotid injection of formalin and is a useful indication that the fixative has reached the electrode site. The blood pressure changed with inhalation of oxygen.

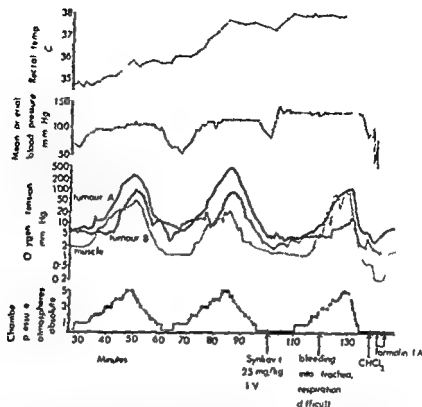


Fig. 13. Experiment 40. Rat with 1 patoma. Two periods of high pressure oxygen inhalation gave similar responses and then Synkavit 25 mg/kg I.V. followed by rather reduced responses in tumour. The formalin effect on tumour and muscle may be noted.

effect of a fall of blood pressure upon tumour oxygen tension. Muscle also has the advantage that there was rarely any trouble due to haemorrhage at the site of the electrode. Records of the effect of inhalation of oxygen under pressure on the oxygen tension in muscle are shown in Figs 5, 7, 9, 10, 11, 12, 13, 14. The oxygen tension of muscle was usually such that fairly full radiosensitivity was present with the animal breathing air.

In Fig. 14, records of the oxygen tension in bone marrow and testis are also shown. In the case of the testis the values indicate that an increase of radiosensitivity would have occurred during the inhalation of oxygen under pressure. However, too much weight must not be put on an isolated observation in an anaesthetised animal. Measurements of the oxygen tension in brain were made in three experiments in which electrodes were inserted into brain and held rigidly in place by the stereotaxic instrument built into the pressure chamber (see Fig. 1). The results showed that the oxygen tension in brain rose during the inhalation of oxygen under pressure, as would be expected but did not

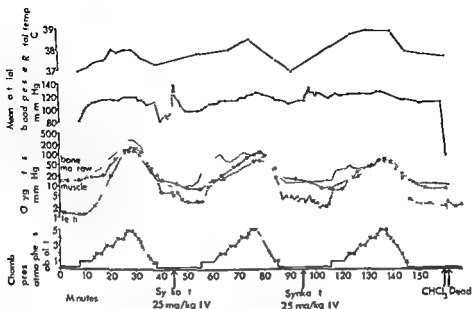


Fig 14 Experiment 47 Effect of high pressure oxygen inhalation on the oxygen tension of bone marrow —  $\Delta$  — muscle and testis — — — — — Synkavit does not appear to have caused much change in the responses to oxygen

tend to diminish when the pressure remained constant at a high level. However, the effect of inhalation of high pressure oxygen on the oxygen tension of various parts of the brain requires detailed investigation.

#### *General effects of high pressure oxygen therapy*

The increase of mean systemic blood pressure which occurred in these anaesthetised rats and mice has already been mentioned (see Figs 9, 12, 13, 14). Other general systemic effects observed included a marked tendency for the animals to become hyperthermic during inhalation of high pressure oxygen. This can be seen from the records of rectal temperature shown in Figs 5, 7 and 9 to 14. These changes took place in spite of active steps to keep the rectal temperature constant, including running cold water through the coil of copper pipe in the chamber. Hyperthermia above 40°C combined with oxygen at 5 atmospheres absolute was rapidly fatal to rats. Rats and mice anaesthetised with urethane tend to lose body temperature unless warmed; it would thus appear that temperature regulation is impaired by urethane anaesthesia. It was more difficult to keep the mice at a steady body temperature.

In the early experiments a bag of soda lime was placed in the chamber to absorb CO<sub>2</sub>, but the chamber was well ventilated because of small leaks and in the latter experiments the CO<sub>2</sub> absorber was omitted with no deleterious effects.

Death during decompression occurred in some of the early experiments in spite of very slow increase of pressure and slow decompression. In later experiments in which animals were tracheotomised because of carotid cannulation death during the experiment was much less frequent. The presence of extensive zones of pneumonitis in animals dying during the experiment suggested respiratory obstruction. It is possible that during decompression extensive congestion of the nasal mucosa and blockage of the trachea with mucus may have been a cause of pneumonitis and death. Tracheotomy may have eliminated this hazard from the longer and more complicated experiments in the latter part of the series.

### Discussion

The primary object of this investigation was to determine whether hypoxic zones in tumours with a radiosensitivity near to the nitrogen level could be raised to an oxygen tension of 10 mm Hg corresponding to a radiosensitivity about twice that of anoxic tissue by the breathing of oxygen at atmospheric pressure or whether the pressure chamber technique is necessary. From the standpoint of radiotherapy the hypoxic zones in tumour are of great importance and it is interesting that over half the tumour zones investigated showed an oxygen tension of less than 4 mm Hg and would therefore be below the half way point of the increase of radiosensitivity obtainable by oxygen. This is evidence in favour of the hypothesis that hypoxic zones in tumour are an important cause of tumour recurrence after radiotherapy. Some of these hypoxic zones showed useful increases of radiosensitivity when the animals inhaled oxygen at atmospheric pressure, some did not while some showed useful increases of radiosensitivity during inhalation of oxygen under pressures of up to 5 atmospheres absolute. Correlation with the histological appearances of the tumours at the sites of the electrodes suggested that many of these hypoxic tumour zones contained viable tumour cells and therefore at a first analysis high pressure oxygen inhalation during radiotherapy would reduce the recurrence rate.

The detailed statistical analysis of these data involves the correlation of numerous variables including the three types of tumour and the histological grading of the electrode sites into 5 groups varying from good tumour to complete necrosis. A full statistical analysis is being made with the aid of a digital computer and will be the subject of a separate communication. The preliminary results indicate that, while some differences will be found between the three tumour types, these will be small compared with the differences between near necrotic and well vascularized zones in any one tumour type. There is something to be gained from pooling the three types of tumour as it gives a better statistical sample from the clinical standpoint.

The finding that the histological appearance of the electrode site is the most important factor determining the level of oxygen tension at that site was to be expected. The finding that 9 out of 77 electrodes showed a fall of oxygen ten-

sion during inhalation of high pressures of oxygen was unexpected but cannot be dismissed as an incidental finding or due to technical failure of the electrodes concerned. Their behaviour was too consistent for this to be a reasonable explanation. They were situated near necrotic zones and sometimes near macroscopic cavities which might well contain gas compressible during the increase of external pressure, with consequent deformation of the tumour and its capillaries. This seems a possible explanation and the paradoxical effects of 5 HT in jection on these electrodes is consistent with this hypothesis. It is of course possible that the presence of the electrode might accentuate the effect of pressure deformation of the tumour but the general phenomenon, that when gas cavities are present in a tumour high external pressures may cause diminution of capillary circulation cannot be ignored and must be set in the balance against the beneficial effects of high pressure oxygen in radiotherapy.

The importance of tumour blood flow in radiotherapy and chemotherapy cannot be emphasised sufficiently, and the factors which alter tumour blood flow will also affect tumour oxygen tension. CATER *et coll* (1962b) found that tumour oxygen tension often varied directly with systemic blood pressure and was very susceptible to falls of blood pressure. Therefore one good effect of inhalation of high pressure oxygen is the rise of blood pressure and some of the increase of the oxygen tension in tumour may be due to this. GULLINO & GRANTHAM (1962) studied tumours transplanted into the ovary and found that adrenaline and acetyl choline affected tumour blood flow in the opposite sense to the changes produced in systemic blood pressure. In their experiments the effect of hormones on the vessels of the long ovarian pedicle cannot be separated from their effect on the vessels in the tumour. However there is evidence which suggests that the imperfectly innervated tumour vessels may be unduly sensitive to circulating adrenaline, noradrenaline, acetyl choline and 5 HT as CATER *et coll* also found that tumour oxygen tension was reduced by adrenaline and noradrenaline in spite of a rise of blood pressure and by 5 HT although the fall of blood pressure was small. The rise of oxygen tension during oxygen inhalation is a good test of an adequate blood flow to tissues and it is noteworthy that 5 HT abolished this even with 5 atmospheres oxygen pressure. Therefore 5 HT probably caused a profound slowing of tumour blood flow. Under the conditions of the experiment the rise of oxygen tension in muscle is not usually altered and this discounts the suggestion that the oxygen is not reaching the arterial blood because of constriction of the bronchioles (VAN DER BEEK 1962). The difficulty experienced in reversing the 5 HT effect with cyproheptadine in the mouse also suggests profound circulatory stasis in the tumour whereby the antidote may reach the affected vessels only with difficulty.

High pressure oxygen inhalation will be advantageous in radiotherapy only if it increases the oxygen tension and thus radiosensitivity of the tumour while the radiosensitivity of the adjacent normal tissues remains essentially unchanged.



The muscle showed marked rises of oxygen tension but was frequently above the critical level of oxygen tension with the animal breathing air. Our data on bone marrow, testis and brain are insufficient to merit discussion. HOWARD-FLANDERS & WRIGHT (1955) suggested that certain normal tissues, in particular bone and cartilage, might not be at maximum radiosensitivity when the patient was breathing air.

### Acknowledgements

We are indebted to Professor J. S. Mitchell for his constant encouragement and advice and to Dr I. A. Silver of the Department of Veterinary Anatomy for many helpful discussions. Dr D. D. Porteous of the Christie Hospital and Holt Radium Institute, Manchester, very kindly supplied us with tumour bearing mice. Two of us, Dr D. B. Cater and Mrs D. A. Watkinson, were supported by the British Empire Cancer Campaign and one of us, Dr F. I. Schönicke, by the American Cancer Society and Western Reserve University of Cleveland, Ohio. This financial support is most gratefully acknowledged.

### SUMMARY

Oxygen tension in rat and mouse tumours was measured by the oxygen-cathode technique and converted to radiosensitivity by the formula of C. RAY (1961). Of 77 recordings made while the animals breathed oxygen at 5 atmospheres absolute in a specially constructed pressure chamber, 45 reached near maximum radiosensitivity and 9 showed a fall of oxygen tension. Reasons for this are discussed. Factors altering tumour blood flow are also important in radiotherapy. After 5-HT, tumour oxygen tension failed to rise during oxygen inhalation even at 5 atmospheres absolute.

### ZUSAMMENFASSUNG

In Tumoren von Ratten und Mäusen wurde die Sauerstoffspannung mit der Sauerstoffkathodentechnik gemessen und mittels der Formel nach GRAY (1961) in Strahlenempfindlichkeit umgerechnet. Von 77 Messungen, die bei Sauerstoffatmung bei 5 absol. Atmosphären in einer spezialkonstruierten Druckkammer vorgenommen wurde, erreichten 45 nahe zu maximale Strahlenempfindlichkeit während 9 einen Abfall der Sauerstoffspannung zeigten. Die Ursachen hierzu werden besprochen. Faktoren, die die Tumordurchblutung ändern, sind auch für die Strahlentherapie wichtig. Nach 5-HT gelang es nicht selbst während Inhalation bei 5 absol. Atmosphären, die Sauerstoffspannung im Tumor zu erhöhen.

### RÉSUMÉ

La tension d'oxygène dans des tumeurs de rats et de souris a été mesurée par la technique de la cathode d'oxygène et a été convertie en radiosensibilité par la formule de C. RAY (1961). Sur 77 mesures faites pendant que les animaux respiraient de l'oxygène à 5 atmosphères absolues dans une chambre à pression construite spécialement, 45 atteignaient presque le maximum de radiosensibilité et 9 montraient une chute de la tension d'oxygène. Les raisons de ce phénomène sont étudiées. Les facteurs qui modifient le débit sanguin tumoral sont eux aussi importants en radiothérapie. Après 5 HT, la tension d'oxygène ne s'élève pas pendant l'inhalation d'oxygène même sous une pression de 5 atmosphères absolues.

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## A WEDGE FILTER FOR COBALT 60 SUPPLEMENTATION OF CARCINOMA OF THE CERVIX UTERI PREVIOUSLY TREATED BY RADIUM

by

G. R. TAYLOR

The treatment of carcinoma of the cervix uteri by vaginal and intra uterine radium sources is frequently followed by the external application of gamma or roentgen ray fields to supplement the radium dosage in the parametria.

A criticism of many techniques for such supplementation is that they raise a region of non uniform dosage to a higher level of dosage while still preserving the non uniformity of the dose. This is particularly true for gamma or roentgen fields divided by a central lead strip and used in parallel anterior posterior opposition.

The penumbra produced by the extended source of a cobalt unit when a simple rectangular lead block of suitable dimensions is placed centrally across the radiation field, may be used to attain some degree of matching of increasing cobalt and falling radium dosage. However the relatively level peaks, particularly for large cobalt fields when combined with the still falling radium contribution produce a falling total dosage distribution. The usefulness of this method is very limited and may only be used if one accepts a restricted plateau followed by a region of falling dosage which extends to the edge of the radiation field.

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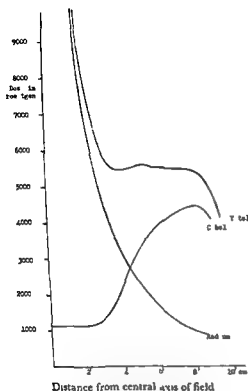


Fig 3 Radium cobalt and combined dosage distributions at the midline of a patient 20 cm thick for a field of  $16 \times 12$  cm

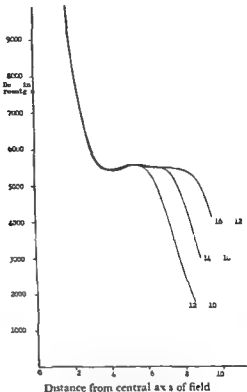


Fig 4 Variation of combined radium and cobalt distributions with distance from the central axis of the field for various field sizes

The radium cobalt and combined dosage distributions at the mid plane of a patient 20 cm thick with the radium centrally placed are illustrated in Fig 3. The combined dosage distributions obtained for field sizes of  $16 \times 12$  cm,  $14 \times 10$  cm and  $12 \times 10$  cm when the cobalt treatment times are adjusted to give a plateau of 5500 r are illustrated in Fig 4. On the same basis the combined distribution curve obtained for a  $14 \times 12$  cm field was virtually coincident with that of a  $14 \times 10$  cm field and is therefore not recorded. Similar combined dosage distributions will apply for other thicknesses of patients as the isodose curves for this wedge maintain their cross field distribution sensibly constant over a range of depths.

Direct addition of cobalt and radium doses was adopted to obtain the combined dosage distributions shown in Figs 3 and 4. It is however clear that as pointed out by TRANIER for the linear accelerator wedge it would be possible to adjust treatment times to achieve the same degree of matching if other assumptions are made as to the mode of summation of dose.



## SUMMARY

A lead wedge filter is described which when suitably placed in the radiation beam ensures that the dose from the supplementary fields is a minimum at points already adequately irradiated by radium and thereafter increases laterally in such a way that it matches the falling radium dosage. A typical combined radium and cobalt dosage distribution is illustrated and the effect of variation in the cobalt field size considered.

## ZUSAMMENFASSUNG

Ein Bleischiebfilter wird beschrieben, das nach korrekter Anordnung im Strahlenkegel die Dose von den Hilfsfeldern an den Stellen, die bereits eine ausreichende Bestrahlung erhalten haben, auf ein Minimum reduziert und das lateral zunehmende Strahlung durch kompensiert der dort abnehmenden Radiumstrahlung. Eine typische kombinierte Radium und Kobalt Bestrahlungsanordnung wird beschrieben und die Einwirkung von Feldgrößenveränderung der Kobaltstrahlung besprochen.

## RÉSUMÉ

Description d'un filtre cunéiforme en plomb qui placé convenablement dans le faisceau de radiation permet de délivrer aux points correctement irradiés par le radium une dose minimale par les champs complémentaires et de donner latéralement une dose croissante compensant la diminution de la dose curiethérapique. Les auteurs présentent un cas typique comme exemple de la distribution de dose combinée par le radium et le cobalt et étudient l'influence des variations des dimensions du champ de cobaltthérapie.

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## INDICATIONS AND METHODS FOR RADIOTHERAPY OF CAVERNOUS HAEMANGIOMAS

A study of 1191 haemangiomas following radiotherapy

by

ULLA BRITA NORDBERG and JAN SUNDBERG

The role of radiation therapy in the treatment of haemangiomas is a subject of keen discussion. Radiotherapy has been used very sparingly in England for example (LISTER 1938, WALTER 1953) because it has been felt that haemangiomas have a natural tendency to spontaneous healing. In Germany, on the other hand, the opinion has been held that the risk of complications such as haemorrhage and infection is so great that a more active attitude is justified (MIESCHER 1944, WEISHAAR & KOSLOWSKI 1959). The Swedish author NOTTER (1956), recommended radiotherapy for haemangiomas in areas where there is an enhanced risk of these complications.

The authors in the present communication examine

1 The results one year following the radiation treatment of haemangiomas and the extent to which these results were affected by such factors as the size of the growths, the quality of radiation used and the dose administered.

2 The effect these same original factors had on the appearances of the skin 5 to 15 years following therapy and whether radiotherapy can be shown to have had any injurious effects.

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Table 1

*Distribution in per cent in the different age group (all patients)*

Year of treatment	Number of patients	Age in years			
		0— $\frac{1}{2}$	$\frac{1}{2}$ —1	1—2	2—10
1945	130	16	33	16	5
1950	274	47	31	20	2
1955	476	61	26	8	1
Total	830	56	29	13	2

Haemangiomas are usually classified in the medical literature according to their histologic appearances into the following categories: haemangioma capillare, haemangioma simplex, haemangioma cavernosum and haemangioma racemosum. This classification, however, is unsuitable for clinical use and at Jubileumskliniken in Lund haemangioma simplex and haemangioma cavernosum are classified on a clinical basis into surface (cutaneous) and deep (subcutaneous) types, two types that commonly occur simultaneously in one haemangioma. The present writers will not discuss haemangioma racemosum and those types of haemangioma capillare known as haemangioma vinosum and angioma stellatum.

### Material

This investigation, which was carried out in 1961, includes all haemangiomas in children under 10 years of age who were given radiotherapy in the years 1945, 1950 and 1955. The number of patients in those years was 130, 274 and 426 respectively, and the number of haemangiomas 169, 402 and 620 respectively, a total of 830 patients with 1191 haemangiomas. Of these haemangiomas 868 (72 %) had only superficial components, 311 (27 %) both superficial and deep elements and 12 (1 %) only deep components.

The size of the haemangiomas showed wide variations. Haemangiomas having a maximum measurement of 15 mm in any direction are called minor; there are 756 minor and 435 major haemangiomas in this investigation. The haemangioma was single in 598 patients, and 232 patients had multiple haemangiomas. The number of haemangiomas per patient in this latter group varied from 2 to 50, the usual number being 2 to 4. The distribution between the sexes is the same as that given in the literature, namely one male to two females.

Table 1 gives the age at the time of the first treatment. The aim has been to treat haemangiomas as early as possible, preferably during the first year of life. The table also shows that the number of patients over the age of one year has diminished with the passage of time, falling from 22 % to 10 % of the total number between 1950 and 1955.

### Investigation and percentage of answers

All patients who were not re examined in 1961, were asked to fill in a questionnaire giving

1 Details of the present appearances of the skin, any changes in the skin in the form of atrophy pigmentation de pigmentation telangiectases, or other abnormality

2 To state in brief whether or not the result was cosmetically satisfactory

3 To state whether they were healthy and normally developed

Certain special problems, however ■ ■ indications and counter indications for radium therapy and the possible occurrence of disturbances in growth due to irradiation of epiphyses, made it necessary for a number of patients to come to the clinic for re examination This examination comprised inspection and palpation with assessment of any permanent changes in the skin and any deformity or hypoplasia in the surrounding tissue Most of the patients also had routine haematologic studies including haemoglobin and red, white and differential blood counts The blood tests were all within normal limits Further investigations such as roentgenography or ophthalmoscopy were carried out where there was reason to suspect that the dose to any one organ was excessive

One hundred and thirty five patients with 178 haemangiomas were requested to come to the clinic, and 695 patients with 1 013 haemangiomas were invited to fill in a questionnaire, some of this latter group elected to come to the clinic for re examination instead Thus a total of 267 patients with 354 haemangiomas (30 % of the total number) were re examined at the clinic and 492 patients with 733 haemangiomas (62 %) filled in the questionnaire This provided data on long term results for 759 patients with 1 087 haemangiomas (92 %) Similar data are not available for 71 patients with 104 haemangiomas (8 %) Some of these latter patients had died but the majority had moved to other districts and could not be traced even by consulting parish registries For 64 of these patients with 96 haemangiomas only a one year control examination is recorded, but not even this is available for 7 patients with ■ haemangiomas

### Principles of treatment

Haemangiomas were treated at Jubileumskliniken during the period covered by the investigation with radium radium combined with contact roentgen therapy or by contact roentgen therapy alone A few patients received roentgen therapy, generally tangentially

The principle followed was that haemangiomas in especially radiosensitive areas, e ■ epiphyses and undeveloped breasts were given contact roentgen therapy The method of treatment was otherwise determined by the depth of the haemangioma and by its spread at the surface Minor superficial haemangiomas received contact roentgen therapy (50 kV, 0.5 mm Al additional

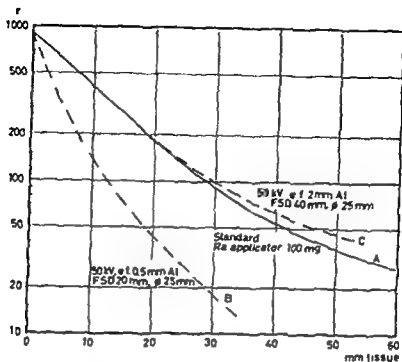


Fig. 1 Central axis depth dose distribution for radium and roentgen contact therapy. Surface dose 900 r.

filter 20 mm FSD corresponding to a HVL of 3 mm soft tissue) Contact roentgen therapy was also often given to major haemangiomas including some where the changes extended down beneath the superficial layers of the skin. The haemangiomas were then compressed during treatment and in some cases the quality of the rays was modified (50 kV 0.5 to 1 mm Al additional filter 40 mm FSD corresponding to a HVL of about 4 to 6 mm soft tissue). Many haemangiomas with relatively thick superficial components were given radium therapy. Haemangiomas with subcutaneous components were mostly treated with radium or in isolated instances with tangential roentgen therapy. Those haemangiomas that showed substantial regression after radium treatment but still had a minor superficial residue were usually given final treatment with contact roentgen therapy. Isolated cases were recommended for surgical therapy if any disfiguring haemangioma residue following radiotherapy existed.

The first radium treatment consisted of a dose of 700 to 800 r at a depth of about 3 mm corresponding to 900 to 1000 r on the skin surface following the method described by STRANDQUIST (1939) (Fig. 1). The radium dose for each additional application for those haemangiomas that received several treatments was usually 500 to 700 r at a depth of 3 mm. The surface dose in

Table 2a

*Results of treatment in per cent for all re-examined haemangiomas*

Total number	Disappeared	After one year		After 5-15 years	
		Almost disappeared	Regression	Disappeared	To surgical therapy
1 087	44	35	21	99	1

Table 2b

*Result of treatment in per cent for all re-examined haemangiomas comparison between haemangiomas without and with deep components major and minor haemangiomas and haemangiomas in males and females*

	Number of haemangiomas	Skin after 11 to 15 years		
		No changes	Minor changes	Major changes
All haemangiomas	1 087	47	48	5
Haemangiomas with only surface components	794	47	49	4
Haemangiomas with deep components	293	42	51	7
Size of haemangiomas	≤ 15 mm	685	43	3
	> 15 mm	402	53	10
Males	357	49	46	5
Females	730	47	48	5

contact roentgen therapy was usually 1 000 r for the first treatment and 600 to 800 r for subsequent treatments

The majority of haemangiomas were treated by one of three methods (routine radiation treatment)

- 1 Radium treatment alone (one or two applications)
- 2 One radium application followed by one contact roentgen therapy treatment
- 3 Contact roentgen therapy alone (one or two treatments)

A minority of growths were treated by other methods (non routine treatment) Some of these were given radium treatment or contact roentgen therapy three times A number received one or more radium applications combined with one or more contact roentgen therapy treatments the first treatment consisting alternately of radium and contact roentgen therapy A few haemangiomas received roentgen therapy generally tangential The interval between the treatments was generally about 180 days occasionally about 120 days and rarely more than 200 days

An examination of the percentage distribution between the different types of treatment described above reveals that 53 % of the haemangiomas received some kind of radium treatment on at least one occasion whereas 45 % were

Table 3

*Result of treatment in per cent for different age groups (routinely treated haemangiomas)*

Age in years	Number of haemangiomas	Haemangioma after one year			Skin after 5 to 15 years		
		Disappeared	Almost disappeared	Regression	No changes	Minor changes	Major changes
0— $\frac{1}{4}$	30	49	38	13	45	51	4
$\frac{1}{4}$ —1	273	17	33	11	51	47	2
1—2	128	56	30	14	47	49	4
2—10	21	31	49	20	62	26	12
Total	952	50	36	14	50	47	3

given contact roentgen therapy only and 2% received roentgen treatment. The number of patients receiving radium therapy has gradually declined during the latter part of the 1950's (NORDBERG 1961) and the number treated with contact roentgen therapy has increased. Treatment to day is mostly by contact roentgen therapy.

Since many patients had more than one haemangioma and since the therapeutic technique and the results obtained vary for different haemangiomas on the same patient, the percentage figures cited above, and the figures in all the following tables refer to the number of haemangiomas and not to the number of patients.

### Results

**One year results** All the haemangiomas that were re-examined have been assigned to one of three groups with the assistance of the case notes (Table 2). The first group (disappeared) consists of haemangiomas that had completely disappeared, the second (almost disappeared) contains those in which only minor haemangioma residues were discernible, the third group (regression) contains those that had receded to a greater or lesser degree but not completely. This last group also includes the 12 cases (1% of the material) that were later referred for surgical therapy. The percentage distribution within the three groups specified in the 96 haemangiomas in which only the one year results are known is 41, 30 and 29% respectively.

**Long term results** As there is no haemangioma residue remaining after 5 to 15 years, the long term assessment applies to the appearance of the skin, i.e. the long term results from the cosmetic point of view. The first group (no changes) contains those cases in which the skin was completely normal, the second (minor changes) contains those in which the skin showed isolated telangiectases, slight pigmentation or depigmentation. The cosmetic results in both these groups were satisfactory. There were more obvious changes in the skin in the third group (major changes).

Data on the long term results for 1 087 haemangiomas, 952 of which re

Table 4

*Results of treatment in per cent after different treatments and different doses (routinely treated haemangiomas)*

Table 4a—one treatment

Treatment	Surface dose in r	Number of haemangiomas	Haemangioma after one year			Skin after 5 to 15 years		
			Disappeared	Almost disappeared	Regression	No changes	Minor changes	Major changes
Radium	≤ 900	56	47	41	12	57	38	5
	> 900	99	61	30	9	66	31	3
Roentgen contact therapy	≤ 900	46	68	24	8	74	24	2
	> 900	262	74	24	2	51	47	2

Table 4b—two treatments

Treatment	Surface dose in r at the 1st treatment	Number of haemangiomas	Haemangioma after one year			Skin after 5 to 15 years		
			Disappeared	Almost disappeared	Regression	No changes	Minor changes	Major changes
Radium	≤ 900	66	32	31	37	41	55	4
	> 900	97	36	40	24	49	46	5
Roentgen contact therapy	≤ 900	34	40	43	17	59	38	3
	> 900	147	31	50	19	35	62	3
Radium + roentgen contact therapy	≤ 900	87	30	53	17	40	57	3
	> 900	58	37	52	11	55	43	2

ceived routine radiation treatment are available. A survey of the long term results for all the radiotherapeutically treated haemangiomas that were re-examined irrespective of the type of treatment they had received is given in Table 2b. Haemangiomas with subcutaneous components are also placed in this table in juxtaposition to those without such components for comparison. Both the one year results and the long term results are considerably worse for the subcutaneous category. There is also as can be seen from Table 2b, a marked difference between major and minor haemangiomas both in the one year and long term results. There is no difference between the results for males and those for females.

The results for haemangiomas that received routine radiation treatment are better than those for the total number of haemangiomas irrespective of the type of treatment. This may be explained by two factors.

1 The majority of the haemangiomas receiving non routine treatment were given three or four treatments and thus received larger skin doses than



Table 5

*Result of treatment in per cent after different treatments and different sizes of haemangiomas (routinely treated haemangiomas)*

Table 5a—one treatment

Treatment	Size of haemangiomas in mm	Number of haemangiomas	Haemangioma after one year			Skin after 5 to 15 years		
			Disappeared	Almost disappeared	Regression	No changes	Minor changes	Major changes
Radium	≤ 15	102	63	31	6	70	28	2
	> 15	53	44	39	17	47	45	8
Roentgen contact therapy	≤ 15	252	74	23	3	56	42	2
	> 15	56	68	30	2	47	50	3

Table 5b—two treatments

Treatment	Size of haemangiomas in mm	Number of haemangiomas	Haemangioma after one year			Skin after 5 to 15 years		
			Disappeared	Almost disappeared	Regression	No changes	Minor changes	Major changes
Radium	≤ 15	84	50	33	17	50	47	3
	> 15	79	18	39	43	42	52	6
Roentgen contact therapy	≤ 15	116	40	43	17	43	55	2
	> 15	65	22	56	22	34	62	4
Radium + roentgen contact therapy	≤ 15	80	38	53	9	54	45	1
	> 15	65	27	52	21	37	58	5

those treated in the normal manner. A greater number of skin changes due to radiation may therefore be expected in this group.

2 When haemangiomas that had received non routine treatment i.e. 12 % of the total material, are excluded the cutaneous group diminishes by 9 % and the subcutaneous group by 22 %, minor haemangiomas by 7 % and major ones by 21 %. It is therefore evident that major haemangiomas and haemangiomas with subcutaneous components are over represented in the non routine groups. These types of haemangiomas give a less satisfactory cosmetic result than minor haemangiomas and haemangiomas with only cutaneous components.

The non routine treated haemangiomas form a non homogenous group as far as the therapeutic technique is concerned. There are also relatively few of them compared with those that had routine radiation treatment. With due consideration to these factors it was therefore thought correct to omit non

Table 6

*Comparison between the one year result and the long term result in per cent for different sizes of haemangiomas (routinely treated haemangiomas)*

Number of haemangiomas	Size of haemangioma, in mm	Haemangioma		Skin after 5 to 15 years		
		After one year	After 5 to 15 years	No changes	Minor changes	Major changes
323	≤ 15	Disappeared	Disappeared	57	41	2
153	> 15	"	"	31	67	2
206	≤ 15	Almost disappeared	"	62	37	1
146	> 15	"	"	37	60	3
54	≤ 15	Regression	"	52	39	9
70	> 15	"	"	36	44	20

routinely treated haemangiomas in further tables. Tables 3, 4, 5 and 6 thus contain only those haemangiomas that received routine radiation treatment.

The results for different age groups may be seen in Table 3. The number of haemangiomas in the 2 to 10 age group is so small that the less satisfactory results in this group are not necessarily significant. There is otherwise no marked difference between the different age groups.

Tables 4a and 4b show the extent to which the results of the treatment are influenced by the size of the dose. Cases that received two treatments (Table 4b) are grouped according to the size of the first surface dose. The boundary between a low and a high dose has been fixed at 900 r. Corresponding depth doses for a normal radium application (A) and contact roentgen irradiation of normal quality (B) are shown in Fig. 1.

Despite the fact that the number of haemangiomas in some groups is rather small, the tables show that for radium treated haemangiomas both the one year results and the long term results are better when the higher dose was given. For haemangiomas that received contact roentgen therapy the long term results are better for those given the lower dose.

The haemangiomas are divided according to size in Tables 5a and 5b, the boundary between the major and minor haemangiomas being fixed at 15 mm as described above. The results of the different types of treatment when given once (Table 5a) or twice (Table 5b) are compared within these two main groups. The results for the major haemangiomas are less satisfactory, those for the different kinds of treatment are basically the same as those shown in Tables 4a and 4b.

The possible variation in the results with the site of the haemangioma was also investigated. Haemangiomas were divided into three main groups: those situated on the head, the trunk and the extremities. The one year results are about the same in all three groups and are similar to the results for all routine

Table 7

*Supplementary examinations — Doses and fractionation time for irradiation of the skeleton, lens and thyroid gland*

Table 7a—Irradiation of the skeleton

Patient's No	Area examined	Dose in rad at the examined part of the skeleton at treatment			Interval in months between treatments		Total dose in rad	Total fractionation time in months
		1	2	3	1-2	2-3		
44 18 24	Thoracic vertebrae	600	500	400	6	8	1 500	14
44 10 13	Cervical vertebrae	900					900	
45 01 18	Wrist	600	600		5		1 200	5
	Skull	600					600	
55 05 03	Femur	70	90		6		160	6
50 06 20	Skull	700	700	400	8	9	1 800	17
49 10 05	Shank	130	90		8		220	8
49 02 06	Thoracic vertebrae	600					600	
49 06 27	Shoulder	200					200	
49 08 23	"	70	70	70	4	6	210	10
50 06 19	Skull	800	500		4		1 300	4
49 10 22	"	800	600		4		1 400	4

Table 7b—Irradiation of the lens

Patient's No	Dose in rad at treatment		Total dose in rad	Total fractionation time in months
	1	2		
50 06 19	90	60	150	4
49 10 22	140	110	250	4
49 12 18	120	100	220	4
49 03 21	100	100	200	4

Table 7c—Irradiation of the thyroid gland

Patient's No	Dose in rad at treatment		Total dose in rad	Total fractionation time in months
	1	2		
45 01 27	90	60	150	5
49 03 23	140	100	240	4
55 09 03	300	75	375	10

radiation treated haemangiomas shown in Table 3. The long term results are better for haemangiomas situated on the head. Of these latter 68 % showed no skin changes after 5 to 15 years and 29 % showed only minor changes. The corresponding figures for the other two groups are 40 % and 42 % respectively without changes and 56 % and 54 % respectively with minor changes. A

Table 8

*Three cases with multiple haemangiomas doses and fractionation periods*

Patient's No	Number of haeman- giomas	Interval between treatments	Dose in rad on			
			Active bone marrow	Thyroid gland	Gonads	Lens
55 03 18	5		9	20	5	70
		3 months	1	0	0	0
		Total	10	20	5	70
50 04 14	15		20		25	
		8 days	20		25	
		4 months	15		40	
		4 months	15		25	
		Total	70	< 20	115	< 10
50 02 13	18		20	80	3	60
		1 day	10	80	0	20
		4 months	10	20	12	20
		4 months	1	10	0	20
		Total	41	190	24	120

relatively larger number of the haemangiomas located about the head were minor ones. This may be one explanation of the fact that the long term results are better for this group than for the other two groups. Another explanation is that the vascularization and thus also the nutrition of the skin is better in the head than in the rest of the body. There is consequently better healing of the skin changes in this region brought about mechanically by haemangiomas and those caused by radiation.

The material was still further divided by specifying the sites even more closely e.g. upper and lower halves of the face and scalp or chest, back and abdomen. The results are essentially the same as that noted for the principal groups within these subdivisions. Such deviations as could be noted are explained by the fact that the number of haemangiomas is small for certain groups.

The relationship between the one year results and the long term results are illustrated in Table 6. No single case with a haemangioma residue was found at control examination after 5 to 15 years (Table 2a) although other skin changes that were to a greater or lesser degree disfiguring were often evident. The haemangiomas are divided in the table according to size and one year results. The results after 5 to 15 years are given for each group and are similar for all haemangiomas except for the group containing those large haeman-

giomas that after 1 year showed only regression. The long term results in this group were often unsatisfactory but for the other haemangiomas the long term results did not differ considerably from the average result. As less satisfactory long term results may be expected for those major haemangiomas that show only regression after one year there is good reason to refer these patients while still in childhood for plastic surgery in order that supplementary non radiotherapeutic treatment may be given at a suitable opportunity.

*Supplementary investigations where complications due to radiation are probable.* There are numerous accounts in the literature of injuries arising from radiotherapy applied to haemangiomas. These injuries usually occur in patients who have been given doses far above those regarded as permissible at our clinic.

Table 7 deals with a number of patients in whom supplementary investigations in connection with their re-examination were performed. The table shows the dose at each treatment, the interval between the treatments and the total dose. The doses are given in rads to make it possible to add doses of differing quality.

*The radio sensitivity of epiphyses,* i.e. the lowest dose at which the risk of growth disturbances or other damage to epiphyses arises, has often been discussed (MAU 1953, FISCHER 1955, WEISHAAR & KOSLOWSKI 1959, BOYSE & GRAF 1960). It is generally stated without any precise information on the quality of the radiation being given that the risk of any permanent growth disturbances is slight after a maximum tissue dose of 300 r during one treatment. WEISHAAR & KOSLOWSKI stated that tolerance increases with fractionation and diminishes with harder radiation. These two writers believed that the tolerance limit stated is also applicable to contact roentgen therapy. A tissue dose of  $> 400$  r produces a risk of the development of deformities.

Twelve patients among those who came to the clinic for re-examination and in whom the tissue dose in some part of the skeleton was high, were subjected to roentgen examination for the detection of possible skeletal changes caused by radiation. It was not possible to demonstrate any deformities or damage to the skeleton even though the dose at a single treatment was as high as 900 rad and the total dose reached 1 800 rad over a 17 month period (Table 7a).

The danger of causing a radiation cataract when treating haemangiomas near the eye was discussed by e.g. MERRIAM & FOCHT (1957), QUIST & ZACHAU CHRISTIANSEN (1959) and BEK & ZAHN (1960). A single dose of about 200 rad gamma radiation to the lens is considered to be dangerous. The longer the fractionation period the greater the tolerance and thus the limit of tolerance is considered to be 550 rad fractionated over a period of three months. Four patients were examined by an ophthalmologist. The lens had been given a total dose varying between 150 rad and 250 rad with a

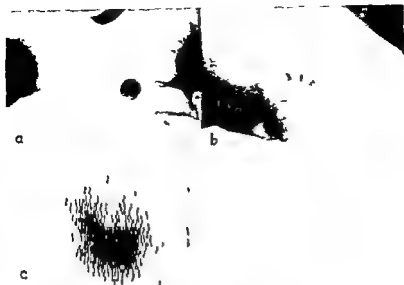


Fig 2 a) Appearances of haemangioma before radiotherapy b) State of skin at control examination with (c) scintigram and radioiodine tracer tests dose administered  $75 \mu\text{Ci}$  thyroid uptake 2 hrs 23% thyroid uptake 24 hrs 47% urine excretion 0-24 hrs 33%

fractionation period of 4 months (Table 7b) There were no signs of radiation cataract in any instance

There appears to be no reference in the literature to the radiosensitivity of the thyroid gland in children The general opinion is however that this organ is relatively insensitive Three patients of the present series were examined by means of radio iodine tracer tests and scintigrams The tissue dose in the thyroid gland was estimated at 150 240 and 375 rad respectively (Table 7c) The tracer studies in all three patients were within normal limits Using these methods of detection a dose of 375 rad apparently caused no changes in the thyroid gland The appearances before treatment from a case of this type are shown in Fig 2 including the present state the scintigram and the radioiodine test

Hypoplasia or aplasia of the female breast after radiation treatment in childhood has been reported in a few papers (RUBE 1954 GREGL & WEISS 1962 inter alia) The authors agree on the high radio sensitivity of the breast anlage but no definite information is yet available on the tolerance limit Among 27 females in whom the haemangiomas were situated near a mamilla two presented evidence of slight mammary hypoplasia The appearances of one of these haemangiomas before treatment and in its present state is shown in Fig 3 The doses to the breast tissue in these two patients could be estimated at 580 and 1150 rad respectively given in one treatment and in two treatments with an interval of 4 months respectively

There is no definite indication for early treatment of haemangioma situated in other parts of the body.

Contact roentgen therapy appears to be superior to radium therapy from both the theoretical and the practical points of view. Radium therapy implies total body irradiation for both patient and staff and ought therefore to be avoided (NORDBERG 1961). Contact roentgen therapy is easier to apply. The duration of the treatment is a matter of seconds, during which time the child and the roentgen tube can be fixed in relation to each other so that the field of treatment is strictly defined. If the extent of the beam is strictly limited, the total irradiation is kept at a minimum for both patient and staff.

Practically all haemangiomas that receive radiotherapy should therefore be given contact roentgen therapy. The majority of haemangiomas with subcutaneous extensions may also be treated successfully by compression of the haemangioma and, if necessary, modification of the quality of the rays to for example, 50 kV 2 mm Al additional filter, FSD 40 mm. This quality has a HVL that is about that of 8 mm soft tissue and has, as is shown in Fig. 1, a depth dose distribution that practically corresponds to that of a normal radium applicator. Fifty-eight haemangiomas with subcutaneous components in the present material were given contact roentgen therapy and 136 haemangiomas of this type received radium therapy. After one year 43% and 40%, respectively, had disappeared completely and 26% and 24%, respectively, were incompletely cured whereas at the time of the control examination 40% and 47%, respectively, showed no changes in the skin and 3% and 7%, respectively, were cosmetically unsatisfactory. It is only very seldom therefore that radium therapy is indicated. A few haemangiomas with large deep components may require roentgen treatment which should, if possible, be tangential.

The surface dose at the first treatment should be 800 to 900 r for contact roentgen therapy. WALTER (1953) has shown that a lesser dose gives worse one year results. A dose of 400 r gives only 9% healing compared with 45% for a dose of 800 r. A higher dose, of say 1 000 to 1 500 r may produce more rapid healing but at the same time the cosmetic result will be worse (HULTBERG 1943 and WALTER 1953 *inter alios*), there will be an increase in pigmentation, depigmentation and atrophy of the skin. The frequency of haemangiomas that showed no skin changes whatsoever at reexamination in the present material was three times greater when the surface dose during treatment was  $\leq 900$  r than when the dose was  $> 900$  r (Tables 4a and 4b).

### Conclusions

- 1 Radiotherapy is not generally indicated for the treatment of haemangiomas
- 2 Rapidly growing haemangiomas on the face should be treated early

for functional, psychologic and cosmetic reasons Haemangiomas in the perineum and adjoining regions should also be treated early because of the risk of infection and ulceration

3 Haemangiomas should be treated in principle with contact roentgen therapy of a quality adjusted to the deepest component of the haemangioma, a HVL corresponding to 3 to 8 mm soft tissue

4 The suitable surface dose for the first treatment is 800 to 900 r

## SUMMARY

The results of radiation treatment of 1191 haemangiomas in 830 patients have been re-examined with special reference to changes in the appearances of the lesion one year later the appearances of the skin 5 to 15 years following therapy and the possibility of injurious effects from the treatment

## ZUSAMMENFASSUNG

Eine Untersuchung der Resultate nach radiologischer Behandlung von 1191 Hämangiomen bei 830 Patienten wurde ausgeführt. Spezielles Interesse wurde folgende Faktoren gewidmet: das Aussehen des Hämangioms ein Jahr nach der Behandlung, das Aussehen der Haut 5 bis 15 Jahre nach der Behandlung und die Möglichkeit von schädlichen Wirkungen der Behandlung.

## RÉSUMÉ

Les auteurs ont ré-examiné les résultats du traitement par les radiations de 1191 hémangiomes chez 830 malades. Ils ont particulièrement étudié les modifications de l'aspect de la lésion au bout d'un an, l'aspect de la peau 5 à 15 ans après le traitement et la possibilité de lésions dues au traitement.

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Most data obtained to date pertaining to these effects have been derived from acute exposure to high doses or radiation. Moreover, until recently almost all experimental work was carried out with roentgen rays whose energy spectra differ from those emitted by the principal radioisotopes. From these studies the conclusions arrived at are often irrelevant to the problem of low dose rate chronic irradiation, and are thus misleading.

It is therefore essential to design irradiation facilities with these specific problems in mind.

*Characteristics of facilities for chronic irradiation:* The facility should be able to deliver a fairly wide range of dose rates. Both long continuous irradiations (several weeks), and accurately timed short exposures (a few minutes), should be attainable. Large target volumes are also required.

Very large units installed in specially designed buildings or restricted areas are very useful, but there is ample justification for an apparatus that can be used in a pre-existing room of normal size and construction, with minimum additional shielding.

Finally, the conditions of irradiation should be reproducible at intervals of several months or even years.

Comparable basic principles found in all existing facilities are as follows:

- 1 Use of moderate quantities of monochromatic high specific activity gamma emitters with long half life e.g.  $^{60}\text{Co}$  and  $^{137}\text{Cs}$  (DESAIN et coll. 1957),
  - 2 Large radiation field volume relative to the target size,
  - 3 Target in normal environmental conditions during long exposures.
- These facilities can be broken down into three broad categories:

**I Self contained,** i.e. target is placed within the confines of the facility  
e.g. gammacell 220 containing 16 000 curies  $^{60}\text{Co}$  produced by Atomic Energy of Canada, Ottawa, 6 curies  $^{60}\text{Co}$  and 5 curies  $^{137}\text{Cs}$  irradiators at the Physics Department, Institute of Cancer Research, Royal Cancer Hospital, London (QUASTLER et coll. 1959).

**II Transportable external beam,** i.e. source is only shielded in one position in the storage container at which time it is transportable.

e.g. 4 000 curies  $^{60}\text{Co}$  irradiator at Cornell University, NY, USA  
215 curies  $^{137}\text{Cs}$  irradiator at the Department of Agriculture, Harrow, Ontario,  
50 curies  $^{60}\text{Co}$  irradiator at the Bunting and Best Institute of Medical Research, University of Toronto.

(The unit described in this article also falls into this category.)

**III Fixed external beam,** i.e. source is stored in a permanent location when in the safe position.

e.g. 11 curie  $^{60}\text{Co}$  irradiator at Division of Biological and Medical Research,

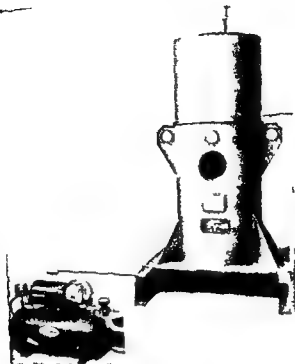


Fig 1 Overall picture of the unit

Argonne National Laboratory, Argonne Illinois U S A (SACHSE et coll 1955) 1 340 curies  $^{60}\text{Co}$  irradiator at the Texas Engineering Experimental Station College Station Texas U S A (RANDALL 1958)

*Technical description* The irradiation facility herein described is a low dose rate transportable external beam unit designed and constructed by the Commercial Products Division of Atomic Energy of Canada Ltd It was installed at the Faculty of Medicine of Laval University Quebec and loaded on November 28th 1961 with 73 6 curies of cobalt 60 (Fig 1)

The source itself comprises 1 mm diameter by 1 mm long nickel plated cobalt 60 pellets having an initial specific activity of approximately 163 5 curies/g

These pellets are sealed by welding into a stainless steel capsule which in turn is welded into a second capsule of the same material thereby giving a double seal and ensuring maximum protection against contamination

The sealed source is mounted in a lead filled steel encased drawer and is held in position by a triarc ring (Fig 2)

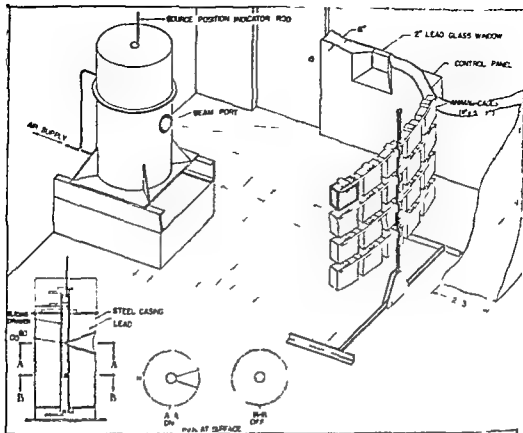


Fig 2 Outline of unit and room showing surface radiation fields

The drawer which has a teflon seal at either end slides vertically in the central bore tube of a cylindrical storage container which is also comprised of lead encased in steel  $1/4$  (6.4 mm) thick (Steel encasement provides protection against fire hazard)

When the drawer is at the bottom of its travel in the bore tube, the source is completely surrounded by a minimum of 7.5 inches (19 cm) of lead. The external fields at the surface are shown in Fig 2. In this position the unit can be used as its own shipping container. The total weight of the unit is 2,400 lbs (approx 1,100 kg).

When the drawer is in the upper position the source stops directly opposite a 38° conical port allowing a collimated beam of radiation to be projected into the shielded room.

The drawer movement is achieved by the application of air pressure at either end. The operating pressure of 25 psi is supplied by a small compressor.



Fig 3 Control console and lead glass window

and reservoir tank of commercial design. It is introduced to either end of the bore tube via two normally closed solenoid valves. Needle valves on the outlets of the solenoid valves can be adjusted to vary the exhaust rate of air from the bore tube, and hence the speed of drawer travel. A third normally open solenoid valve in the upper line acts as a safety device such that in the event of a break in the electrical circuit or a power failure pressure is immediately applied to the top of the drawer returning it to the safe position.

Mechanical support for the drawer in the source exposed position is provided by a solenoid actuated pin which engages in a groove around the drawer body at the same time closing the lower solenoid valve. This enables long irradiations to be carried out without maintaining air pressure in the drawer. A cable attached to one end of this pin extends outside the shielded room enabling manual retraction in the event of solenoid failure.

The facility is operated from a control console outside the shielded room which houses a timer, power supply control and source position indicator lights (Fig 3).

The timer has a range of 120 hours in increments of 6 minutes, the minimum setting being 18 minutes. Shorter exposures can be achieved by manual shut off of the timer.

*Installation and room shielding.* For economical reasons it was considered necessary to install the unit in a room requiring minimum additional shielding and security measures. Such a room was selected in the basement of the Faculty of Medicine (Figs 4 and 5) situated in a corner of the central wing of the building, the occupancy of adjacent areas being almost nil.

The concrete floor rests directly on bedrock and the two preexisting outside walls already offer considerable radiation protection. Above the ceiling an



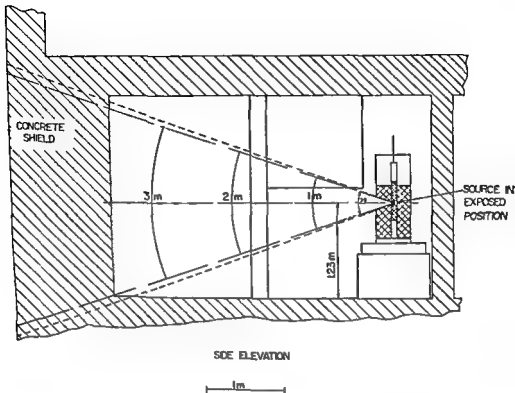


Fig 5 Room projection in a vertical plane

of reinforced concrete in the exterior wall of the building. The average half value layer of concrete for  $^{60}\text{Co}$  gamma rays being 5 cm, the total thickness of 130 cm corresponds to 26 HVL and offers a dose reduction factor of more than  $10^7$  (WACHSMANN 1957). Accordingly, no radiation above background level could be detected outside the building. In order to avoid the necessity of filling in the outside window, a concrete wall 20 cm thick has been built in the path of scattered radiation. The inside protection wall, not being exposed to any direct radiation, is also 20 cm thick. Viewing is carried out through an  $8 \times 8$  (20  $\times$  20 cm) 2 (5 cm) thick high density lead glass window which gives a maximum angle of vision of  $110^\circ$  (shown in Fig 4).

A standard door containing a  $5/32$  (4 mm) thick layer of lead provides access to the shielded room and is interlocked with the unit in such a manner that the source cannot be raised into the exposed position with the door open. Alternatively, opening of the door during an irradiation will immediately return the source to the safe position in less than 2 seconds.

Both window and door frames contain layers of lead insuring adequate shielding.

The irradiation dose in mr/h at various positions in the control room, when the unit is operating, is given below (position letters refer to Fig. 4)

	A mr/h	B mr/h	C mr/h
At the floor level	1	2	3
1.23 cm above floor level	3	4	6
Behind the lead glass window		2.5	

The field (2.5 mr/h) at the console is not increased when the door is open, therefore the door interlock can be disconnected (in exceptional circumstances) and the unit operated without closing the door. (All the above measurements were taken on March 30th 1962 with an A F C I Multipurpose survey meter.)

*Animal cages and rack* Rectangular cages,  $8 \times 8 \times 5$  ( $20 \times 20 \times 12.5$  cm), constructed from 18 g galvanized steel mesh with the entire front hinged for access, contain the animals (rats) during the irradiation.

These cages are mounted on a steel framework such that the centre of each cage lies on a point on the surface of a sphere 3 metres in radius. By this means, the average dose rate at the center of each cage is constant at 10.6 r/hour (on June 20th, 1962) with a uniformity of  $\pm 5\%$  across the 12.5 cm width.

*Dosimetry* In all applications of ionizing radiations one important aspect is that of the accurate measurement of the amount of energy absorbed by the objects undergoing irradiation.

In laboratory facilities the object source relationship is generally fixed which permits the dose rate in the sample to be deduced. This is done by using a plot of the gamma field in air over the irradiation volume in conjunction with the absorption properties of the material.

For subsequent irradiations over a period of time allowance is made for the decay in the activity of the source which can be accurately determined at any time after the original calibration (HOOVER et al. 1955).

An alternative method and one which eliminates any possibility of error, is the use of dosimeters, several types of which are currently available. Two examples are ionization chambers and the ferrous/ferriic system.

*Material and methods* Preliminary measurements were made on the 7th and 8th of February 1962 using a 70.5 medium energy Victoreen condenser chamber of 25 r capacity, covered with a lucite cap to obtain a wall thickness suitable for  $^{60}\text{Co}$  gamma rays. Readings were made with a 'model 70' Victoreen condenser meter.

Complete measurements were made between the 16th and the 26th of April using high energy Victoreen chambers (models 552 of 2.5 r capacity, and 553 of 25 r capacity) having a nominal wall thickness of 450 mg/cm<sup>2</sup>. The readings were made with a 'model 570' r meter. At this time the source strength was approximately 70 curies.

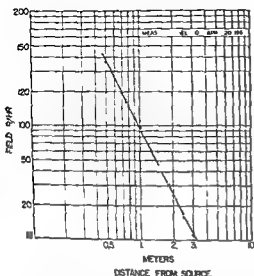


Fig. 6 Dose rate (as on 20th of April 1967) in function of the focal distance along the central beam

Both systems had been calibrated less than 1 month before the measurements

At all positions, three 5 min exposures were made using the chamber having the most appropriate range generally these readings differed by much less than the  $\pm 5\%$  rated accuracy. The means were calculated and correction made for the 'chamber factor', temperature and atmospheric pressure

### Results

*Doses in the axis of the beam* Fig. 6 shows excellent agreement between the two series of measurements for points situated within 2 m from the central axis (The figures of the first series are multiplied by 0.975 to correct for the radioactive decay)

It will be seen from the data below that between 70 and 300 cm focal distance there is also good agreement with the inverse square law

Distance in m	Square of the distance	Dose rate in r/h	r/h $\propto 1/D^2$
0.5	0.25	363	90.75
0.7	0.49	195	95.50
1	1	99.5	99.50
1.5	2.25	41	99
2	4	24	96
2.5	6.25	15.4	96.25
3	9	10.6	95.40
3.5	12.25	8.6	105.35

The dose at 50 cm is too low but an error of 1 cm in the estimated focal distance is sufficient to explain this value. The dose at 350 cm is too high this



measurement was made a few centimeters away from the wall and there is obviously significant backscattering at that location.

It can be seen that taking an average value of 97.5 for the product of the equation at the end of April, we had by chance in the beginning of February for intermediate focal distances the relation  $\text{dose } \propto (\text{distance in m})^2 = 100$ .

In the future this value will decrease directly with the decay of the source activity taken as 100% on the 5th of February, 1962. The approximate dose-rate (in r/h) at any focal distance and at any time can therefore be readily estimated.

It is noteworthy that although this irradiator was especially constructed for chronic low dose rate irradiation of a large target area its simple design makes it suitable for the irradiation of small objects at a very short focal distance i.e. with a high dose rate e.g. at a focal distance of 20 cm (at the nozzle of the collimator), the maximum field diameter is 14 cm. It can be seen, applying the previous formula that an object the size of a Petri dish can be irradiated at a dose rate of approximately

$$x = \frac{100 \times (100)^2}{(20)^2} = \frac{10^6}{4 \times 10^1} = 2,500 \text{ r/h}$$

or 41.7 r/min (in February 1962). Likewise at a distance of 2 cm an object approximately 1 cm<sup>3</sup> can be exposed to a dose rate of about  $25 \times 10^4$  r/h or 416.7 r/min. However secondary radiation from the irradiator may be expected to influence the dose rate for samples placed inside the collimator and the irradiation cannot any more be considered as coming from a point source for focal distances shorter than 20 cm. The last figures are therefore only a rough guide and will be supplemented by chemical dosimetry done with each experiment.

This irradiator is therefore useful for a number of applications ranging from the chronic exposure of large biological objects to radiochemistry.

*Field size* The limits (in the horizontal and vertical planes) are indicated in Figs 4 and 5. The homogeneous utilizable beam is defined as the region where there is a maximum  $\pm 5\%$  variation in dose rate between points situated on a spherical surface at equal distances from the source.

The penumbra is the region just outside the beam where the dose rate falls to less than 5% of its full value (this being the smallest percentage change measurable by the dosimeters).

The in situ measurements showed a very well defined utilizable beam with a narrow penumbra. The homogeneous beam covers an angle of  $39^\circ$  in the horizontal plane and  $38^\circ$  in the vertical plane (Figs 4 and 5). These values are in keeping with the calculated  $38^\circ$  angle of the collimator. Taking the penumbra into account, the total beam covers  $42^\circ$  in the horizontal plane  $40.5^\circ$  in the vertical plane. The horizontal axis is at a slight angle to the end wall the area of which is covered by the homogeneous beam being a 'distorted circle'.

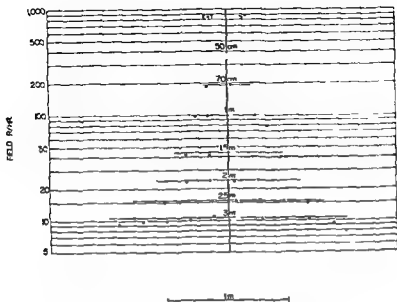


Fig 7 Lateral variation of the dose rates for various focal distances

with a radius varying from 122 to 130 cm and surrounded by a corona of penumbra 10 cm in width. Lines showing the limits of the field and the projections of its axis have been painted on the walls.

*Lateral variation of the dose* Fig 7 shows that there is very little lateral dose rate variation in a horizontal plane, situated 123 cm above floor level for focal distances of 70 to 300 cm.

Fig 8 shows measurements taken along vertical lines 1, 2, 3 and 3 1/2 m away from the source in the central beam. The focal distance along these lines increases from the centre towards floor and ceiling and the dose rate diminishes accordingly. However, the curvature of the isodose lines is small past 2 m focal distance which means that a parallelepipedic cage arrangement can be used if one is satisfied with a dose variation of  $\pm 10$  to 15 % from one cage to the other.

### Practical utilization

This apparatus lends itself to two conditions of irradiation at first thought beyond the limitations of a cobalt irradiator: (1) exactly reproducible dose rates at the same focal distances for long periods of time; (2) continuously variable dose rates simulating exposure to fallout gamma irradiation.

The first is achieved by a composite filter made of a number of thin copper

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$$\propto \frac{100}{20^2} = \frac{100}{4} = \frac{10^2}{10^2} = 2.500 \text{ r/h}$$

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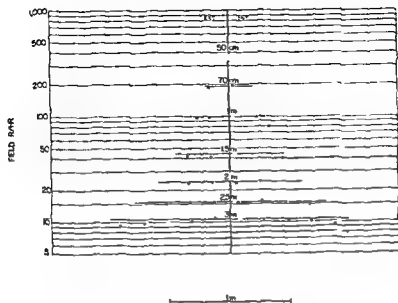


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The first is achieved by a composite filter, made of a number of thin copper

Fig. 8. Variation of the dose rate along central lines in the focal plane.

and aluminum layers designed to compensate for the decay of the radioactive emitter.

The complete filter placed in front of the collimator will absorb 50% of the radiation, therefore giving an output similar to that without filter or  $^{60}\text{Co}$  half life later (i.e. 5.3 years).

This half life corresponds to a decay of about 1% per month. Thus by removing every other month a copper layer of appropriate thickness, it will be possible to obtain dose rates reproducible within 2% for more than 5 years, for each focal distance.

The second is achieved by a carriage moved at a continuously variable speed along the central beam, enabling us to deliver, to animals, doses of radiations simulating that of exposure to fallout gamma irradiation. The intensity of this irradiation, after a fairly short build up period, decreases as a power function of time. Our fallout simulator is derived from the comparable assembly built by BAKER at the University of Toronto (BAKER et coll. 1961).

Both composite filter and variable speed cage carrier are presently under construction and will be described in a forthcoming paper.

Biological work utilizing this equipment has just started and the first experimental results indicate that the LD 50/30 days of Sprague Dawley rats is almost double for a chronic irradiation over a period of 4 days compared with an acute exposure (20 min duration) to  $^{60}\text{Co}$  rays (GIBBS et coll. 1962).

## SUMMARY

In view of the ever increasing interest in the effects of fallout and chronic irradiation of living organisms it has become necessary to have facilities individually designed to carry out such studies. Basic design principles are discussed and the technical description of one such irradiator designed and built at moderate cost is outlined. Detailed isodose curves measured with the unit in situ are presented. A method for using the irradiator to simulate fallout irradiation conditions is given and the results of the first biological experiments are quoted.

## ZUSAMMENFASSUNG

Um dem ansteigenden Interesse über die Wirkungen von Atomausfall und chronischer Bestrahlung auf den lebenden Organismus gerecht zu werden ist es nötig, überspezielle individuell gepragte Einrichtungen zu verfugen die solche Studien zulassen. Die Grundprinzipien hierzu werden diskutiert und die technische Beschreibung eines solchen Strahlers der zu moderatem Preis gebaut werden kann umrissen. Detaillierte Dosiskurven die mit dem Apparat in situ gemessen wurden werden gezeigt. Eine Anwendungsart des Strahlers unter Bedingungen die bei Atomausfallstrahlung herrschen wird gegeben und die Resultate der ersten biologischen Experimente sind zusammengefasst.

## RÉSUMÉ

L'étude des effets des retombées radioactives et de l'irradiation chronique d'organismes vivants suscite de plus en plus d'intérêt. Nous discutons les principes de réalisation d'irradiateurs spécialement adaptés à ces études et décrivons un tel appareil construit à prix très modique. Nous donnons le relevé détaillé de la dosimétrie faite avec l'appareil «in situ». Nous indiquons comment cet irradiateur pourra être utilisé pour simuler l'exposition à la composante de retombées radioactives et mentionnons les résultats des premières expériences biologiques faites au moyen de cet appareil.

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## L'EMPLOI DE LA GEOMETRIE DESCRIPTIVE POUR LOCALISER LES SOURCES DE RADIUM, DE RADON ET DE RADIOISOTOPES ARTIFICIELS À DES FINS DE DOSIMÉTRIE

par

JEAN MARC ESCOFFÉ

Il y a plusieurs années PATERSON et PARKER (*in* MEREDITH 1947) et QUIMBY (1953) introduisirent deux plans de répartitions géométriques de sources de radium et de radon. Depuis l'avènement des radio-isotopes artificiels plusieurs auteurs ont étudié la dosimétrie pour diverses répartitions géométriques de ces sources concrètes (BERCA 1958, 1962; BERCA et coll. 1958; DUTREIX 1961; FRITZ et coll. 1960; FROST 1960; MISHAM et coll. 1954; PIERQUIN et coll. 1959; SHALEK et coll. 1957; WAMBERSIE et coll. 1958).

Tous ces plans, cependant, peuvent se ramener soit à l'idée de dosimétrie uniforme préconisée par PATERSON et PARKER, soit à celle de sources uniformément distribuées de QUIMBY. Les tables de PATERSON, PARKER et de QUIMBY, peuvent parfois être utilisées pour d'autres radio-isotopes si l'on emploie les correctifs de HALF (1958).

Dans tous les cas de radiothérapie interstitielle et d'applications intra-cavitaires, il est toujours désirable de vérifier si la dosimétrie de la distribution

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spatiale obtenue correspond bien à celle projetée. Des renseignements à ce sujet peuvent être obtenus de deux manières générales, notamment au moyen de mesures et au moyen de calculs.

### 1 Les mesures peuvent être directes (A) ou indirectes (B)

*A Les mesures directes* se font au moyen d'un détecteur approprié, placé à la surface extérieure ou intérieure du corps près de l'ensemble des sources. Les renseignements obtenus de cette façon sont très limités, cependant.

*B Les mesures indirectes* peuvent être effectuées à la suite de la reconstruction des sources réelles. Cette reconstruction peut être obtenue à partir de deux radiographies prises sur un ou deux films. Il va sans dire que la reconstruction de sources réelles constitue un certain danger.

### 2 Les calculs

Il a été démontré avec les années que parmi les méthodes dosimétriques les méthodes graphiques sont les plus précises et les plus utiles. Une fois que la répartition géométrique est connue, les calculs sont effectués à partir de tables appropriées. Les méthodes actuelles d'obtenir cette distribution spatiale sont les suivantes.

*A Localisation à partir d'une seule pellicule radiographique* La méthode du foyer déplacé (LEDERMAN et coll. 1948) ne requiert qu'un seul radiofilm. Elle a été modifiée par TESTA (1957) afin de permettre les calculs de l'intensité en chacun des points d'intérêt sans que la reconstruction préconisée par ces premiers ne soit requise.

Plus récemment, une nouvelle technique n'exigeant aussi qu'un seul film a été présentée. Cette méthode tomographique, cependant, ne s'applique qu'à des cas idéaux et quasi idéaux, tels que dans les cas d'aiguilles parallèles (EGAN et coll. 1960, PIERQUIN et coll. 1960, 1962, SHALEK et coll. 1957, STOVALL et coll. 1962). De plus, une section unique ne donne des renseignements qu'à cet endroit et non pas pour l'ensemble de la région traitée. Pour cette raison, ces chercheurs ont, en général, pris plusieurs sections.

*B Localisation à partir de deux films* Un bon nombre d'auteurs ont découvert des moyens de trouver la répartition de sources concrètes en se servant de deux radiographies orthogonales (FARR 1953, MEREDITH 1947, SMITH 1958), c'est-à-dire à angle droit. Quelques-uns ont reconstruit l'ensemble des sources au moyen de sources postiches, mais la plupart ont déterminé la répartition sans avoir recours à la reconstruction. La méthode de calcul est parfois simplifiée par des nomogrammes (HOLT 1956), calculateurs et dispositifs de toutes sortes.

En général, ces méthodes de localisation spatiale nécessitent suffisamment de calculs; de plus, elles n'évoquent pas toujours les vues que nous désirons obtenir. Afin de remédier à ces difficultés, une nouvelle méthode est proposée ci-bas. Elle a comme base la géométrie descriptive. Quoique cette méthode nous permette d'obtenir toutes les vues spatiales, quelles qu'elles soient, les vues les plus utiles aux fins de dosimétrie sont celles de profil et de bout.



*Définition et historique de la géométrie descriptive* La géométrie descriptive (LANDREAU 1919) est la partie des mathématiques appliquées qui a pour but de représenter exactement sur un plan, les figures de l'espace et de résoudre à l'aide de la géométrie plane les problèmes ou l'on considère les trois dimensions.

On peut faire remonter les méthodes et les applications de la géométrie descriptive à la plus haute antiquité mais on peut dire que c'est à MOYSE que revient la gloire d'avoir débrouillé le chaos des procédés graphiques employés avant lui dans les arts industriels et d'avoir systématisé les procédés en un petit nombre de principes dans la géométrie descriptive qu'il enseigna à Paris en 1794 et 1795.

### Technique de la méthode proposée

Un support de bois (Fig. 1) tenant deux cassettes à angle droit a été construit. À l'endroit où les deux cassettes se rencontrent, une tige métallique a été placée en permanence. Cette tige a pour but d'indiquer par la suite, au moyen de sa projection sur chaque film, l'orientation d'un film par rapport à l'autre.

2. Un radiosfilm est placé dans chacune des deux cassettes. Au moment des deux radiographies orthogonales, les cassettes seront alternativement insérées à l'intérieur du support de bois.

3. Le patient est placé de sorte que les sources concrètes puissent être radiographiées sur les deux films perpendiculaires sans que le patient ne se déplace entre les deux expositions. Les sources devront être aussi près que possible des deux films.

4. Un anneau de laiton (ou d'un autre métal dense) est placé sur le patient à une distance anneau-film égale à la distance sources-film vertical. La radiographie latérale est ensuite prise à une distance foyer-peau suffisamment grande, (1 m environ) afin de rendre la distortion et le grossissement au minimum. Sans que le patient ne se déplace, l'emplacement de l'anneau est ensuite vérifié et déplacé si nécessaire de sorte que cette fois-ci il soit à une distance anneau-film égale à la distance sources-film horizontal. Une radiographie verticale est ensuite prise à une distance d'environ 1 mètre.

5. Les deux pellicules sont développées et les grossissements de l'ensemble des sources sont déterminés pour chacune des deux images à partir du rapport

$$\frac{\text{Dimension maximale de l'image de l'anneau}}{\text{Diamètre réel de ce même anneau}}$$

Leurs calques sont obtenues sur deux feuilles de papier de soie différentes.

6. Ensuite, à partir de ces deux facteurs de correction et d'un pantographe adéquat, les deux images sont réduites à leur vraie grandeur sur ces deux feuilles de papier de soie différentes.

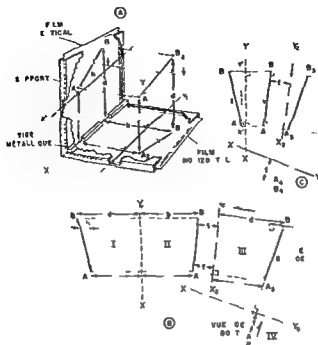


Fig 1 La vraie longueur  $AB$  et la vue de bout  $A_1B_1$  d'une source linéaire unique s'obtiennent à partir des radiographies à l'angle droit corrigées de leur grossissement

7 Ces deux images corrigées telles qu'obtenues sur les deux feuilles de papier de soie sont placées au dessus d'une visionneuse. L'une de ces images est déplacée par rapport à l'autre de sorte que les projections de la tige sur chaque film, coïncident ou soient parallèles et que des lignes tirées entre les sources ponctuelles (ou les extrémités de chacune des aiguilles ou des tubes) correspondantes des deux films soient perpendiculaires aux images des bords superposés de la tige métallique. Comme exemple dans la Fig 1 B la vue I est placée relativement à la vue II, de sorte que les lignes  $A_1A_2$  ainsi que  $B_1B_2$  soient perpendiculaires à  $X_1Y_1$  (la superposition de l'image de la tige sur chacun des films après avoir été corrigée du grossissement).

8 Les vues de profil et de bout (ou de face) sont obtenues

9 A partir des tables appropriées l'intensité des rayonnements est déterminée pour l'endroit désiré

### Exemples

#### 1 Source linéaire unique (Fig 1)

Celle-ci est considérée en vue d'expliquer en détail les fondements de cette méthode graphique. Une fois que les sept premières étapes de la section II ont été suivies il s'agit ensuite d'obtenir les vues de profil et de bout. Fig 1 (A) montre l'aiguille  $AB$  quelque part dans l'espace



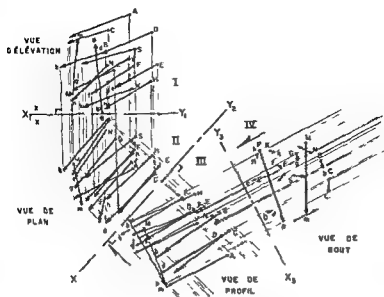


Fig 2 La longueur III et la base IV efficaces de l'implantation cylindrique proviennent de l'application des principes de la première figure

A partir de chacune des extrémités des aiguilles de la vue II on trace des lignes de rappel perpendiculaires à la ligne de terre  $X_2Y_2$  tout en la traversant

Le long de ces nouvelles lignes de rappel on rapporte à partir de la ligne de terre  $X_2Y_2$  et au-delà de celle-ci les distances entre chaque extrémité d'une aiguille donnée de la vue I et la ligne de terre  $X_1Y_1$  tel qu'il a été fait dans le cas de l'aiguille unique (Fig 1). Tout en employant les mêmes lignes de terre et les lignes de rappel appropriées ce procédé est répété pour chacune des autres aiguilles. On obtient ainsi les paires de points a A b B c C etc (vue III).

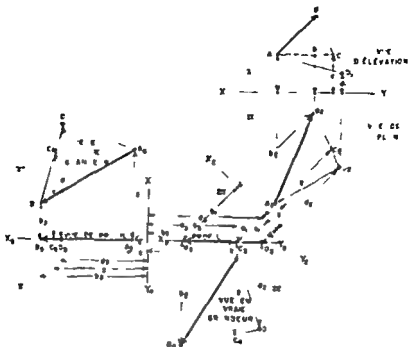
Cette dernière vue ainsi obtenue en tirant les lignes aA bB cC etc est une vue de profil de l'implantation d'aiguilles puisque la moyenne des aiguilles est vue en vraie grandeur.

**Vue de bout.** Une ligne de terre  $X_3Y_3$  est tracée perpendiculairement et à une distance quelconque de l'ensemble des aiguilles de la vue III qui forment les côtés latéraux de l'implantation cylindrique. Tout comme auparavant cette orientation effective est déterminée au moyen de la feuille de papier quadrillé placée sur la visionneuse.

Perpendiculairement à  $X_3Y_3$  et traversant cette nouvelle ligne de terre on trace des lignes de rappel émanant de chacune des extrémités des aiguilles de la vue III.

À partir de cette ligne de terre  $X_3Y_3$  et au-delà de celle-ci on rapporte pour chacune des aiguilles les distances entre chaque extrémité d'une aiguille de la vue II et la ligne de terre  $X_1Y_1$ . Ces distances sont mesurées le long de ces nouvelles lignes de rappel. Ceci nous donne les points a A b B c C etc de la vue IV ainsi construite.

Tirons les lignes aA bB cC etc afin de mieux voir les aiguilles dans cette vue IV qui est la vue de bout.



A partir de B et de D<sub>2</sub> traçons des lignes de rappel perpendiculaires à  $\lambda_2\lambda_2$

Le long de ces lignes de rappel rapportons les distances  $a_1$ ,  $b_1$ ,  $c_1$  et  $d_1$ . Ceci nous donne les points A<sub>2</sub>, B<sub>2</sub>, C<sub>2</sub> et D<sub>2</sub> (vue III)

Puisque la ligne A<sub>1</sub>C<sub>1</sub> avait été construite parallèlement au plan horizontal c est à-dire que les côtés  $a_1$  et  $c_1$  sont égaux il en suit que A<sub>2</sub> et C<sub>2</sub> coïncideront en un seul point

Puisque AC (qui se trouve dans le plan ABD) est vue comme un point A<sub>2</sub>C<sub>2</sub> dans la vue III il en suit que cette projection III est une vue de profil

*Vue en vraie grandeur* Traçons une ligne de terre  $\lambda_2\lambda_2$  à une distance quelconque de B<sub>2</sub>A<sub>2</sub>D<sub>2</sub> et parallèle à cette vue de profil. Dans la figure 3  $\lambda_2\lambda_2$  a été prise à une distance nulle de B<sub>2</sub>A<sub>2</sub>D<sub>2</sub>.

A partir des points A<sub>2</sub>, B<sub>2</sub>, C<sub>2</sub> et D<sub>2</sub> traçons des lignes de rappel perpendiculaires à B<sub>2</sub>A<sub>2</sub>C<sub>2</sub>D<sub>2</sub> ou  $\lambda_2\lambda_2$ .

Rapportons les distances  $a_2$ ,  $b_2$ ,  $c_2$  et  $d_2$  le long des lignes de rappel correspondantes. Ceci détermine les points A<sub>4</sub>, B<sub>4</sub>, C<sub>4</sub> et D<sub>4</sub>.

Tirons les droites A<sub>4</sub>B<sub>4</sub>, A<sub>4</sub>D<sub>4</sub> et B<sub>4</sub>C<sub>4</sub>D<sub>4</sub>.

Cette nouvelle vue IV obtenue en regardant le plan B<sub>2</sub>A<sub>2</sub>C<sub>2</sub>D<sub>2</sub> perpendiculairement est la vue en vraie grandeur du triangle ABD.

*Dosimétrie* Puisque A<sub>4</sub>B<sub>4</sub>D<sub>4</sub> représente le triangle ABD vu en vraie grandeur la vraie distance perpendiculaire entre D et AB peut être mesurée sur la vue IV. De plus nous pouvons mesurer à quelle distance du centre de l'aiguille AB cette ligne perpendiculaire se trouve.

De ces données et des connaissances de la source radio-active la dose au point D peut être déterminée en employant les tables appropriées.

La dosimétrie au point D peut être obtenue directement de la vue IV si nous possédons l'isodose de l'aiguille.

*Remarques* Dans la Fig. 3 deux vues auxiliaires (vue de profil et vue en vraie grandeur) ont été ajoutées. Ces projections permettent de mieux voir comment fonctionne la géométrie descriptive. Elles aideront aussi à mieux saisir les vues de la figure 4.

Prolongeons la droite B<sub>2</sub>A<sub>2</sub>C<sub>2</sub>D<sub>2</sub> et traçons une ligne de terre  $\lambda_4\lambda_4$  perpendiculaire à cette première droite.

Rapportons au-delà de  $\lambda_4\lambda_4$  les distances prises entre la ligne de terre  $\lambda_4\lambda_4$  et les points A<sub>2</sub>, B<sub>2</sub>, C<sub>2</sub> et D<sub>2</sub> qui la précèdent.

Puisque ABCD apparaît dans la vue III comme une ligne B<sub>2</sub>A<sub>2</sub>C<sub>2</sub>D<sub>2</sub>, il en suivra que la vue de bout de cette projection donnera une autre vue de profil B<sub>4</sub>C<sub>4</sub>D<sub>4</sub>.

Tirons une ligne de terre  $\lambda_5\lambda_5$  parallèle à la droite B<sub>4</sub>C<sub>4</sub>D<sub>4</sub>.

Traçons les lignes de rappel perpendiculaires à  $\lambda_4\lambda_4$ . Ces droites sont tracées à partir des points B<sub>4</sub>, C<sub>4</sub>, D<sub>4</sub> et A<sub>4</sub>.

Rapportons les distances  $b_4$ ,  $c_4$ ,  $d_4$  et  $a_4$ .

Tirons les lignes A<sub>4</sub>B<sub>4</sub>, A<sub>4</sub>D<sub>4</sub> et B<sub>4</sub>C<sub>4</sub>D<sub>4</sub>.

Cette nouvelle vue VI est la vue en vraie grandeur du triangle ABD et elle est identique à la vue IV. Comparer les deux vues.

Il est à noter que la vue IV n'a pas été employée ici puisqu'elle ne se trouve pas sur le chemin entre les vues V, VI et les deux premières vues.

#### 4 Implantation plane de grains radio actifs (Fig. 4)

Les vues I et II représentent le film vertical (la vue d'élévation) et le film horizontal (la vue de plan) après que les sept premières étapes de la technique ont été suivies. Les grains sont représentés par les lettres a, b, c, d, e, f, g, h, i, j, k et l.

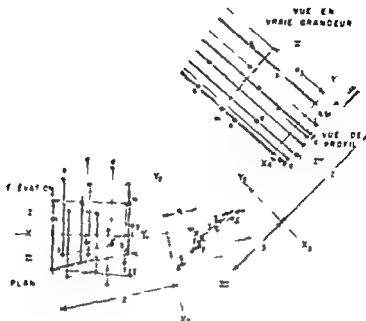


Fig 4 La vue d'face  $V$  d'une implantation plane de grains réel ou actif est obtenue en trouvant d'abord une vue de profil  $V_2$  effective

*Vue de profil* Dans la vue d'élévation prenons trois points (grains) deux vers l'extrême droite ou gauche et un autre à l'autre extrémité

Tirons les lignes entre ces 3 points qui sont pris suffisamment espacés

A partir du point  $a$  traçons une droite parallèle à la ligne de terre  $X_1Y_1$  et rencontrant la ligne  $e_k$  en  $m$  (vue I)

De  $m$  (vue I) abaissons une ligne de rappel perpendiculaire à  $X_1Y_1$  et rencontrant  $e_k$  en  $n$  (vue II)

Dans cette vue II tirons la nouvelle ligne  $am$  et prolongeons la. Cette nouvelle ligne  $am$  (vue II) est en vraie grandeur puisque dans la vue I la ligne  $am$  avait été prise parallèle à  $X_1Y_1$  c'est-à-dire que la projection orthogonale  $am$  (de la ligne  $AM$  appartenant au triangle  $ACM$  de l'implantation plane située quelque part dans l'espace) sur la vue d'élévation est parallèle à la ligne de terre  $X_1Y_1$

Le long du prolongement de la ligne  $am$  (vue II) traçons une nouvelle ligne de terre  $X_2Y_2$  perpendiculaire à  $am$  de la vue II

Au-delà de  $X_2Y_2$  et le long du prolongement de  $am$  de la vue II rapportons les distances entre les points  $a$  et  $m$  (vue I) et  $X_1Y_1$ . Les nouveaux points  $a$  et  $m$  (vue III) coïncident donc en un seul et unique point puisque les distances rapportées ( $a_1$ ) sont identiques

A partir de chacun des points de la vue II traçons des lignes de rappel perpendiculaires à  $X_2Y_2$  et rapportons y les distances entre les points de la vue I et la ligne de terre  $X_1Y_1$

Cette vue III est une vue de profil de l'implantation plane des grains  $A, B, C, D, E, F, G, H, I, J, K, L$  pourvu que l'implantation se trouve sur un plan idéal. Ceci est vrai puisque les points  $A$  et  $M$  sont vus en un seul et unique point

*En général* les grains ne sont pas sur un plan idéal. Dans ce cas les grains ne paraissent pas sur une ligne droite dans la vue III. En telle situation la vue III est plutôt une approximation

de la vue de profil la déviation étant d'autant plus grande que le triangle formé par les trois grains arbitrairement choisis n'est pas parallèle au plan efficace des grains. Pour réduire cette erreur au minimum regardons de bout le plan (vue III) de grains qui est quelque peu tourné sur lui-même autour de la forme allongée qui forme l'ensemble des grains de la vue III. Cette nouvelle vue nous donnera une vraie vue de profil.

Traçons une ligne de terre  $\lambda_2 Y_2$  perpendiculaire à la forme allongée des grains de la vue III et à une distance quelconque de ceux-ci.

A partir de chacun des points (vue III) traçons des lignes de rappel perpendiculaires à  $\lambda_2 Y_2$  et traversant celle-ci.

Rapportons à partir de  $\lambda_2 Y_2$  les distances entre les points de la vue II et la ligne de terre  $\lambda_2 Y_2$  comme il a été fait pour le grain A.

Cette nouvelle vue IV est une vue de profil.

*Iue en vraie grandeur* Traçons une ligne de terre  $\lambda_4 Y_4$  perpendiculaire à la forme longitudinale de l'ensemble des grains de la vue IV. Cette ligne est prise à une distance quelconque de l'ensemble des grains de la vue IV.

A partir de chacun des grains (vue IV) traçons des lignes de rappel perpendiculaires à la ligne de terre  $\lambda_4 Y_4$  et allant au delà de celle-ci.

Pour chacun de ces grains rapportons les distances entre les points de la vue III et  $\lambda_2 Y_2$ , tel qu'il a été fait pour le point A (distance  $a_2$ ).

La nouvelle vue V est la vue en vraie grandeur (vue de face) de l'implantation plane.

*Dosimétrie* Maintenant que l'axe de l'implantation est connue (vue V) la dose à la région traitée s'obtient à partir des tables du système de dosimétrie choisi.

### 5 Application de radium intracavitaire — cancer du col utérin (Fig. 5)

Fig. 5 montre les vues d'élévation et de plan d'un tandem et de deux tubes radio-actifs lesquels proviennent chacun d'un groupe de tubes situés dans deux ovoïdes différents. Le tandem pointe vers le bas dans la vue d'élévation parce que dans cette application l'utérus a été renversé.

La vue I représente la vue d'élévation. Cette vue de l'image corrigée du grossissement s'obtient en prenant une radiographie orthogonale sur un film vertical en la réduisant au moyen du pantographe. Nous pouvons aussi obtenir cette vue en se servant de la méthode de TESTA. Contrairement à cette première méthode la double exposition sur un même film nous donne la vue de plan en plus.

La vue de plan représente la projection non grossie du tandem et des deux tubes sur un plan horizontal.  $\lambda_1 Y_1$  représente la ligne de terre entre ces deux vues.

*Localisation des deux points A par rapport au tandem* Les deux points A (indiqués comme A III A afin de les distinguer) seront localisés d'après la plus récente définition (MILLER 1962) de ce point. Tout d'abord nous devons obtenir le plan vertical passant par le tandem vu en vraie grandeur.

Traçons une ligne de terre  $\lambda_2 Y_2$  parallèle à l'image du tandem dans la vue (II) de plan et à une distance quelconque.

A partir des deux extrémités du tandem et des deux tubes (vue II) traçons des lignes de rappel perpendiculaires à  $\lambda_2 Y_2$  et allant au delà de cette ligne de terre.

Le long de ces lignes de rappel rapportons les distances correspondantes entre les extrémités du tandem de la vue I et  $\lambda_1 Y_1$ , c'est-à-dire les distances  $a_1$  et  $b_1$ . Traçons cette ligne.

Ceci donne un plan vertical contenant le tandem en vraie grandeur (vue III). Comparer à la figure 1.



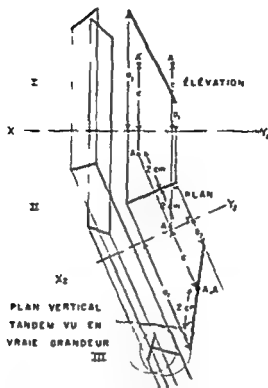


Fig 5 Les deux points, A peuvent être localisés dans les plans vertical I et l'horizontal II lorsque nous avons déterminé le plan vertical passant par le tandem vu en vraie grandeur III et la projection des tubes des deux ovales sur ce plan

Rapportons aussi au-delà de  $N_2Y_2$  les distances entre chaque extrémité des tubes de la vue I et  $N_2Y_2$ . Tirons les lignes dans cette vue III

Ceci donne les projections des tubes sur le plan vertical (vue III)

Autour de ces tubes de la vue III traçons les surfaces extérieures des ovales

À partir de la moyenne de ces surfaces extérieures traçons une ligne perpendiculaire au tandem vu en vraie grandeur et rencontrant celui-ci (vue III)

À partir de cette intersection mesurons (deux) 2 cm le long du tandem vu en vraie grandeur tout en s'éloignant des deux ovales. Ceci détermine les deux points A

*Dosimétrie du tandem* La dosimétrie aux points A (A et A) peut maintenant être déterminée pour ce tandem puisque de la vue III (plan vertical vu en vraie grandeur) nous pouvons mesurer à quelles distances ces deux points A se trouvent des bouts du tandem. Aussi nous savons que les points A se trouvent à une distance perpendiculaire de 2 cm de celui-ci

*Points A et A dans la vue de plan* Partant de AA de la vue III traçons une ligne de rappel perpendiculaire à  $N_2Y_2$  et traversant celle-ci et le tandem de la vue II

Le long de cette ligne de rappel déterminons les points A et A' en les plaçant à 2 cm de chaque côté du tandem (vue II) Ceci est justifié par la définition des points A la droite tirée entre ces deux points A et passant le tandem perpendiculairement se trouve parallèle au film horizontal

*Points A et A' de la vue d'élévation* Partant des points A et A' de la vue (II) de plan traçons des lignes de rappel perpendiculaires à  $X_1Y_1$  et allant au-delà de celle-ci

Le long de ces lignes de rappel rapportons à partir de  $X_1Y_1$  la distance entre A et  $X_1Y_1$  et celle entre A' et  $X_1Y_1$  = est à-dire les distances  $c_1$  Ceci détermine nos deux points A (A' = A) dans la vue d'élévation

*Dosimétrie des tubes des ovaires* Les deux points d'intérêt A et A' sont donc situés par rapport aux deux ovaires pour les vues d'élévation et de plan

Construisons 4 paires de triangles au moyen des deux tubes et des deux points A des vues d'élévation et de plan Pour chacune des 4 paires de triangles répétons le procédé de la figure 3 tout en employant la même ligne de terre  $X_1Y_1$

*Remarques* Il existe une méthode plus simple de localisation Elle est généralement justifiable due aux grandes distances entre un tube choisi et chacun des points A Dans cette méthode nous prenons les sources linéaires comme étant ponctuelles De cette façon l'on est ramené à obtenir 4 lignes en vraie grandeur (la droite entre le point central d'un tube et un point A)

Pour obtenir ces quatre lignes il s'agit de répéter la procédure de la figure 1 quatre fois Les lignes de terre (sauf  $X_1Y_1$ ) seront cependant différentes pour chacun de ces quatre cas

Une fois que ces 4 distances sont obtenues en vraie grandeur les intensités peuvent être obtenues à partir des tables en tenant compte du nombre total des tubes dans chacun des ovaires

Une fois que l'on connaît suffisamment les méthodes de géométrie descriptive nous pouvons soustraire quelques étapes

A l'une des extrémités de  $A_1B_1$  (Fig. 1) rapportons perpendiculairement à  $X_1B_1$  la différence des hauteurs (cotes) des points  $B_1$  et  $A_1$  viz la distance d = c L'hypoténuse mesurée est la distance en vraie grandeur entre les points A et B situés quelque part dans l'espace

## Discussion

Nous remarquons de la figure 1 que le support de bois n'est pas requis pourvu que le bord du film vertical soit parallèle au dessus de la table et que le cote latéral du film horizontal soit parallèle au cote latéral de la table

VREELAND a déjà donné une méthode de correction pour la distortion d'images sur les radiofilms Celle-ci est négligeable si les conditions suivantes sont mises en pratique

- 1 Grande distance foyer sources
- 2 Courte distance film sources
- 3 Épaisseur et largeur de l'ensemble des sources petites par rapport à la distance foyer film
- 4 Anneau et sources à distance égale du film
- 5 Films bien placés et faisceaux suffisamment perpendiculaires aux films
- 6 Patient non déplacé entre les deux expositions

Lorsque les grossissements pour les deux films sont identiques il n'est pas nécessaire de réduire chacune des deux images. Il suffit tout simplement d'en tenir compte dans les dimensions finales avant de reporter aux tables et isodoses.

Les tables de radium citées (GLANIER et coll. GRESSEFF et coll., MEREDITH VERHAGEN) sont presque toutes calculées à partir des données de SIEVERT (1932). Les tables du système de Manchester (MEREDITH 1947) ont été refaites par JOHN (1961) elles ont été multipliées par le facteur

$$\frac{1}{0.965} \frac{8.1}{8.25} = 1.033$$

Ces nouvelles tables tiennent maintenant compte de la plus récente valeur de l'activité spécifique d'une source ponctuelle de radium (ATTIX & RITZ 1957). Elles sont alors exprimées en

$$\frac{\text{mg li}}{1000 \text{ rad}}$$

On remarque dans la méthode de géométrie descriptive décrite que toutes les distances rapportées le long des lignes de rappel proviennent de la deuxième vue précédente ou la deuxième suivante si l'on revient en arrière. Les distances rapportées pour obtenir la vue III proviennent de la vue I, celles de la vue IV proviennent de la vue II, etc.

Dans tous les exemples cités la convention habituelle de letterer n'a pas été suivie. Les indices ont été choisis d'une telle façon qu'en rapportant les distances les indices des points et de chaque ligne de terre soient les mêmes. Comme exemple,  $r_1$  est la distance entre le point  $A_1$  et la ligne de terre  $A_1A_2$ ,  $r_2$  est la distance entre  $A_2$  et  $A_2A_3$ . Les lignes de terre étant conventionnellement pointillées sont ici généralement représentées par des lignes trinitées.

Toutes les implantations d'aiguilles parallèles ainsi que celles de grains formant des cubes du type BERG (BERG 1958 et BERG et coll. 1958) se résolvent en suivant l'exemple du cylindre (Fig. 2).

La précision de la méthode a été déterminée pour des implantations non idéales d'aiguilles postiches et de grains non radio-actifs. Les variations maximales des dimensions finales étaient de 5 %.

## RÉSUMÉ

Une méthode graphique de localisation des sources radio-actives est décrite. Elle est ensuite illustrée pour une implantation cylindrique de sources linéaires, une implantation plane de grains radio-actifs, ainsi que pour une application intracavitaire de radium.

## SUMMARY

A graphical method of localizing radioactive sources is illustrated by means of a cylindrical implantation of linear sources, a single plane implantation of radioactive grains and an intracavitary application of radium.

## ZUSAMMENFASSUNG

Eine graphische Methode für die Lokalisierung von radioaktiven Quellen wird bildlich erläutert und demnach werden eine cylindrische Implantation von linearen Strahlenquellen eine offene Einzel Implantation radioaktiver Körner wie auch eine Übertragung in intra cavitären Radiumquellen illustriert

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## BOOK REVIEWS

BIOLOGISCH CHEMISCHER STRAHLENSCHUTZ EINE ÜBERSICHT IN TABELLEN VON R. Huber und E. Spode Akademie Verlag Berlin 1962 Price 124 DM

The menace of nuclear war and the enhanced risk of radiation accidents by the increasing use of nuclear energy have drawn attention to the possibilities of chemical and biologic protection against radiation injury. The research activity in this field has been extensive and an enormous number of papers have been published although the absence of a bibliography covering the whole field seems conspicuous.

Reports reviewing the literature dealing with attempts to alter the response of animals to ionizing radiation were published as early as 1949 and in 1951 and 1953 by SELLE et coll from the University of California Los Angeles. HUBER and SPODE have now with German thoroughness prepared a survey in tabular form of the works on biologic and chemical radio-protection covering a time period from 1945 to 1959/1960. The large amount of work within this field is illustrated by the number of references close on 1 600. By far the greatest number of investigations have been carried out on the effects of SH compounds and related substances. Bone marrow transplantations play a dominant role among the many attempts to obtain therapy against acute radiation injury. Other substances surveyed include hormones, amino acids, amines, heterocyclic compounds and proteins, alcohols, carbohydrates and organic acids and vitamins and related compounds. Attention is also paid to the influences on the vegetative as well as the central and peripheral nervous system, parabiosis and transfusion, antibiotics and sulphonamides, cyan compounds and other enzyme toxins and antihistamines. The survey appears to be almost complete and will be of great value as a reference to those working in the field of chemical and radiobiologic protectors.

The use of a special device with sharp-edged rings that cut the leaves detracts from the loose leaf system which in itself seems an excellent idea. It is to be hoped that a different kind of cover will be used in the next edition. The price of DM 124 appears to be rather high.

Arne Nelson

THE TOXICOLOGY OF RADIOACTIVE SUBSTANCES Vol. 1 STRONTIUM CAESIUM RUTHENIUM RADON Editors: Letavet and E. I. Kuryandskaya. Translation from the Russian edited by E. Lloyd. 236 pages, 113 figures and 67 tables. Pergamon Press Oxford 1962. Price 100 Sh.

Access to the comprehensive Russian scientific literature has to a great extent been hampered by the language barrier. The increasing number of translations into English has now made this volume available to Western readers who are presented with a full account of Russian progress in the study of the effects of isotopes of strontium, caesium, ruthenium and radon in experimental animals.

The Russian original was published in 1957 and the work reported was carried out from 1931 to 1953. The interpretation of some of the results has been modified by the editors of the English edition in the light of later investigations. Most of the experimental results are however still valid and of great interest in spite of the long time lapse between the appearance of the Russian and English versions.

There are four main sections: (1) Absorption, distribution and excretion; (2) Radiotoxic effects in high dose experiments; (3) Radiotoxic effect of radioactive ruthenium, caesium and strontium in continuous experiments; (4) Stimulation of the excretion of radioactive strontium and caesium from the organism.

KIRYANOVSKAYA emphasizes the importance of studying the reactions of the organism during the continuous internal administration of small doses of radioactive substances. The papers included are therefore mainly concerned with the biologic effects of radioisotopes under continuous intake (2 to 3 years). BIRYKINA reports a much higher retention of ruthenium-106 from the gastrointestinal tract (100 to 200 times higher than that given by certain early American investigators). This difference is probably due to the particular chemical forms used, which especially in the case of ruthenium will complicate the metabolism. KIRANOVSKAYA and USTINOVAYA have studied the transfer of Sr-90 and Sr-90 from mother to foetus in rats and have established that the accumulation of strontium in the foetus is mainly due to the isotope received during pregnancy. This has been confirmed by the reviewer and his co-worker in an investigation in mice which also showed that the foetal uptake coincides with the ossification of the foetal skeleton and begins approximately at the 14th day of gestation. The strontium deposition in the females prior to gestation is of minor importance. It is stated that a subcutaneous dose of Ru-106 gave a more marked distribution of the leukopoiesis and erythropoiesis than Sr-90 and Cs-137. An investigation of the chronic effect of these isotopes administered per os in rabbits revealed, however, that radiostrontium caused more extensive damage to the erythropoiesis than was evident after Cs-137 and Ru-106.

The last part of the book deals with the search for agents that stimulate the excretion of radioactive substances. All the classic methods have been tried with only slight effects.

The book constitutes an excellent review of the extensive work in the U.S.S.R. on the biologic effects of radioactive isotopes. The pictorial material is not uniform; however, the legends give no information on staining, methods or magnification and the few autoradiograms are primitive compared with the standards set by the autoradiograms of ULLBERG and co-workers in this country. Any statistical treatment is conspicuously absent.

Inge Nelson

FILMDOSIMETRIE: GRUNDLAGEN UND METHODEN DER PHOTOGRAPHISCHEN VERFAHREN ZUR STRAHLENDOSIMETRIE. Von Klaus Becker. 176 Seiten, 93 Abbildung u. Springer, Berlin 1962. Preis 24 DM.

A short introduction on the various kinds of radiation and the fundamental concepts of dosimetry is followed by a more detailed account of photographic processes, the properties of different emulsions and developers and densitometry. The main part of the book is devoted to the various methods of photographic dosimetry. Emphasis is laid on radiation protection measurements while other uses are touched upon more lightly. The difficulties and sources of error, especially when measuring radiation of unknown quality or mixed radiations (e.g. gamma rays and neutrons) are discussed in detail and advice given on the precautions that should be observed. Theoretical foundations as well as practical information on film badge design and the organisation of a radiation protection service are considered and discussed in detail.

The book ends with a long and useful list of references. It is however a pity that many papers bear only a code reference consisting of a few letters and figures so that their tracking is difficult without access to a specialized library; an indication of the institutes of origin would have been helpful.

The reviewer considers the book to be of great value to all those working theoretically or practically in the field covered.

Sven Benner

## A MODIFIED COBALT 60 APPLICATOR FOR THE TREATMENT OF RETINOBLASTOMA

by

BENGT H O ROSENCRON and BJORN TENGROTH

Numerous methods for the treatment of retinoblastoma have been proposed during recent decades. The present method of choice is some form of radiation therapy with or without the concomitant administration of radiomimetics.

Retinoblastoma is a malignant tumour arising from the retinal germ cells; it occurs almost exclusively in infancy and childhood and is frequently congenital. Among eye tumours the growth is second in frequency to melanoma of the uvea. The tumour is present in both eyes and often in some 30 per cent of the cases has a multilocular character.

Retinoblastomas are highly malignant and without treatment the prognosis *quo ad vitam* is extremely grave. The tumour may either spread via the optic nerve to the cavity of the skull and orbit or by metastases through the blood paths.

Enucleation until the late 1920's was the only chance of saving the life of an affected child. After FOSTER MOORE in 1929 had introduced therapy with ionizing radiation from radium and particularly after diathermy (WEVE 1932) had come into use attempts were made to treat the less affected eye in cases

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of bilateral retinoblastoma while the other eye was enucleated, in unilateral cases the affected eye was enucleated. Diathermic treatment of the tumour itself (WEISS 1932, DUNN 1937) or photocoagulation of the vessels entering it (MEYER SCHWICKERATH 1939) has occasionally resulted in healing. The risk of recurrence or of large intra-ocular haemorrhages must, however, be deemed comparatively great.

Whereas some workers (REISE et coll. 1955, 1957, 1958) have claimed excellent results with a combination of roentgen irradiation to the eye and parenteral radiomimetic triethylene melamine, (T.M.) therapy, other workers using this mode of treatment (ERICSON & ROSENCRANZ 1961) have failed to achieve equally good results. The intravenous or intra-arterial injection of T.M., owing to its necessarily parenteral administration, must constitute a considerable risk of inducing systemic lesions. The T.M. concentration in the tumour admittedly may become high and the radiomimetic activity adequate, but lesions particularly of the bone marrow, make the use of the drug hazardous. The benefits of T.M. therapy will be realized only in the care of clinicians who have considerable experience of the drug's administration and thorough knowledge of its narrow range of application. Therapy with intravitreal Thioctepa (Tisofyl) injections has been tried (ERICSON & ROSENCRANZ 1961) but it merely produced temporary improvement. Since the interchange between tumour tissue and vitreous is not understood, the Tisofyl concentration in the former cannot be estimated and it probably does not attain the intended level.

Roentgen irradiation to the entire eye suffers from obvious disadvantages. The doses commonly given, 3 000 to 4 000 r (REISE recommended a total dosage of 8 000 r in divided doses of 400 r), have almost invariably been accompanied by cataract formation, frequently by necrosis of the vascular walls leading to intra-ocular haemorrhage, and not infrequently by phthisis bulbi. The limit for the risk of phthisis appears to lie around 5 500 r.

Treatment with radioactive applicators was initiated in 1929 by FOSTER MOORE, who used radon needles inserted into the tumour, and was later modified in various ways (WALDMAN 1940, JOYCE 1941, JOHNSTON 1949). STALLARD (1948) introduced his so-called radium desk — a specially designed radium applicator of platinum formed in a thin shell having the same curvature as the sclera and capable of being sutured to the sclera outside the tumour. This applicator was further modified by substituting the isotope  $^{60}\text{Co}$  for the radium preparation. In 1952, STALLARD surveyed the results of therapy in the series of retinoblastoma cases he had treated over the previous 20 years with both roentgen irradiation and radon needles as well as with radium and  $^{60}\text{Co}$  applicators, the results of corresponding treatment in other workers' series being used as a basis for comparison. He came to the conclusion that treatment with radium and cobalt applicators was preferable to roentgen irradiation of the whole eye when the retinoblastoma covered less than one-



Fig 1 Co applicator with ring for attachment

third of the retina. Effective immobilization of the child's head was absolutely essential when roentgen irradiation was employed. There was a high incidence of late complications in the form of haemorrhages and retinal detachment if the dosage was to be effective.

Radium and cobalt applicators are so shaped that they can be located over the retinoblastoma. Owing to their close proximity to the tumour, they make it possible to expose it to relatively large radiation doses which, decaying geometrically, do not unduly affect surrounding tissues. Only  $\gamma$  radiation is utilized. The results achieved with these applicators indicate that complications are relatively few and rare. The lens receives a comparatively small radiation dosage, a fact which reduced the incidence of cataract in STALLARD'S series.

Pending the advent of better procedures based on entirely new principles, the fact that an applicator can reach a circumscribed retinoblastoma without unduly harming surrounding tissues must make its use the method of choice for the treatment of solitary retinal neoplasms of up to 10 mm in diameter.

Novel therapeutic methods have also been tried. One such method, the electron irradiation of extensive retinoblastomas with lead shielding of the lens, has yielded encouraging results but the number of cases is still too small to justify a final verdict (HULTBERG 1962). BECKER of Heidelberg described another modification. A further interesting possibility is the utilization of the so-called Bragg peak in high energetic proton irradiation.

Progress in the field of retinal surgery has contributed a number of methods and attachments for achieving scleral buckling. One such device, the so-called scleral buckler, has been used routinely for a number of years in our clinic (ROSENGREN 1960). It consists of a ring to which is soldered a curved arm carrying a small ball or cylinder at its free end, the whole assembly being made of silver. In practice, a unit with an arm of suitable length for the application in mind is selected, and the arm is manoeuvred backwards along the bulbar wall extraconjunctivally or transconjunctivally until the ball or

cylinder is located at the required point on the exterior of the bulb. The ring is then fastened around the limbus with a few episcleral sutures when the arm is bent the attached ball or cylinder buckles the sclera. The resultant retinal incurvation is visible in the ophthalmoscope and allows final adjustments to be made. This type of scleral buckler has proved to be especially suited for the treatment of retinal detachment with solitary ruptures.

The scleral buckler has now been modified by replacing the silver ball or cylinder on the arm with a platinum sphere containing  $^{60}\text{Co}$ , thus converting the device into a versatile cobalt applicator (TENCRÖTH 1962). By virtue of the scleral incurvation, the precise position of the applicator may be checked and if necessary corrected under ophthalmoscopic control by bending the arm. The ball or cylinder is thus pressed against and into the base of the tumour. Consequently the tumour will more or less envelope the applicator and the dose will be adequately distributed. As mentioned a series of rings with different arm lengths is available the arms being screwed into a socket in the cobalt sphere (see Figs 1 and 2).

Before one of STALLARD'S  $^{60}\text{Co}$  disks can be applied it is necessary to locate the projection of the tumour on the sclera, a time-consuming procedure. Furthermore attachment of the applicator may require that one or more of the extra-ocular muscles be cut thus prolonging the duration of the operation still more. Lastly, removal of the applicator demands that the posterior bulbar segment be exposed subjecting the subject to the stress of another almost as lengthy session under anaesthesia. Such exposures of the sclera become even more difficult if the patient has previously received irradiation therapy of some kind because the excision of fibrotic tissue called for in such cases is attended by massive haemorrhages in the operation field.

This  $^{60}\text{Co}$  sphere has proved as simple to apply as the scleral buckler. No manifest necrosis has been induced by compression and irradiation of the interposed conjunctiva. A tumour situated in the posterior segment of the eyeball may conveniently be approached by inserting the arm through a minute conjunctival incision, the operation may be made under light anaesthesia. The applicator is removed by first cutting the episcleral sutures around

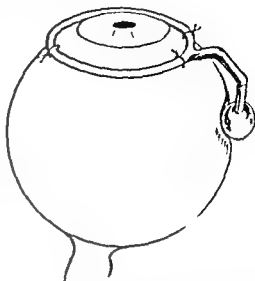


Fig. 2 Principle of attachment of cobalt applicator

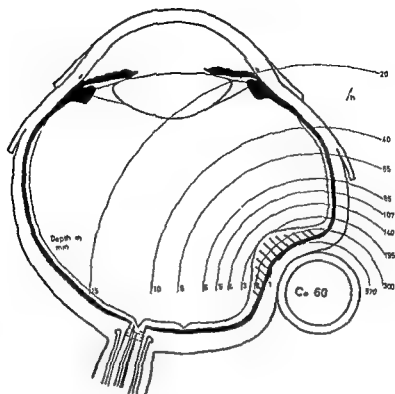


Fig 3 Isodose curves showing dose rate in r per hour

the limbus and then extricating the arm and sphere by a gently twisting movement. This procedure may readily be carried out under local anaesthesia and a  $^{60}\text{Co}$  sphere applied extraconjunctivally may be removed without any anaesthesia whatsoever.

**Radiation data for the  $^{60}\text{Co}$  sphere.** The  $^{60}\text{Co}$  applicator has the shape of a near sphere with an external diameter of 6 mm. An internally threaded hollow stud is provided as a means of attachment to the arm (see Fig 1).

The radioactive cobalt component is enclosed in a 0.5 mm thick platinum shell. The current designs have an activity of 8 mCi (isodoses see Fig 3).

As manufactured the sphere is charged with  $^{60}\text{Co}$  which subsequently has been activated in a neutron reactor at Amersham, England.

Our source has a higher activity as compared to STALLARD's cobalt desk, another dose rate and therefore another fractionation (dose time relationship) is consequently used. The treatment time is about 24 hours giving about 12 000 r at 1 mm depth. This dose seems to be comparable with the 19 000 r administered in about 100 hours by STALLARD.

Table 1

*Doses in r at increasing depth*

Fields	1	2	3+4 (Booster to 1)
Date	11 11 1960	5 1 1961	25 3 1961
Depth in mm	1	12 000 r	6 000 r
	2	6 300 r	3 300 r
	3	4 100 r	2 000 r
	4	3 000 r	1 500 r

Table 2

*Doses in r at increasing depth*

Fields	1	1 a (Booster to 1)
Date	20 9 1960	25 10 1960
Depth in mm	1	10 000 r
	2	5 300 r
	3	3 400 r
	4	2 500 r

### Case reports

*Case 1* Boy aged 3 years with bilateral retinoblastoma. The left eye had been enucleated in another hospital and the right eye had received a total dose of 4 900 r combined with intravenous Tl M administration. The patient was transferred to our eye department because large tumour masses were still present on the fundus. A cobalt sphere was applied for 10 hours in November 1960; dosage particulars are given in Table 1. Two weeks later the tumour was found to be disintegrating. Owing to the discovery of a further tumour arising from another part of the fundus a <sup>60</sup>Co sphere was again inserted for 5 hours in April 1961 (see Table 1) and two weeks later this tumour was much smaller. As a booster dose to field 1 in May 1961 failed to prevent a general recurrence the right eye had to be enucleated.

*Case 2* Girl aged 12 months with bilateral retinoblastoma in whom the fundus had been practically covered with tumour tissue when the left eye was enucleated. A tumour of the right eye 6 optic disk diameters across was treated by repeated photocoagulation of the vessels supplying the tumour and once by diathermy. While this treatment was in progress a large intra-ocular haemorrhage occurred. Somewhat later when the blood had been absorbed the tumour was seen to have grown. At this stage in September 1960 a cobalt sphere was applied, the estimated dose being given in Table 2. The cobalt sphere was re-applied a month later as tumour tissue persisted. After another month the tumour had diminished appreciably, the reduction progressing until the tumour had completely healed. At control examination 26 months later the sole sequela was a retinal scar. The patient's ocular fixation was then adequate with central vision, but on account of her age the visual acuity could not be measured satisfactorily. (The patient was last seen in September 1963.)

*Case 3* Boy aged 12 months with bilateral retinoblastoma whose left eye had been enucleated as the fundus had been almost completely covered by growth. Examination of the right eye disclosed the presence of two tumours of 2 and 4 optic disk diameters respec-

Table 3

*Doses in r at increasing depth*

Fields	I	II	3
Date	21 11 1961	5 12 1961	9 1 1962
Depth { in mm	1	12 500 r	12 500 r
	2	6 600 r	6 600 r
	3	4 300 r	4 300 r
	4	3 100 r	3 100 r

Table 4

*Doses in r at increasing depth*

Fields	I	I a (Booster to I)
Date	18 1 1962	8 5 1962
Depth { in mm	1	10 000 r
	2	5 300 r
	3	3 400 r
	4	2 500 r

tively which were irradiated from a  $^{60}\text{Co}$  sphere. The first focus was treated in November and the second 2 weeks later the doses being similar (see Table 3). A further two weeks later a new third focus measuring 3 optic disk diameters was detected and was treated in a corresponding manner in January 1962. The tumours were appreciably smaller two months later and four months after the last cobalt application exhibited no signs of progression there were no indications of any new foci. Twelve months after the last application the retina merely presented signs of healed foci. There was no evidence of any new tumours or of recurrence in the old scars (August 1963).

*Case 4* Boy, aged 2 years with bilateral retinoblastoma, whose right eye had been enucleated because of diffuse infiltration. A cobalt applicator was positioned in the left eye in January 1962 against a tumour 9 optic disk diameters across which received the doses specified in Table 4. Some 4 months later the retinoblastoma was still present but was distinctly smaller. Another cobalt applicator was introduced on 6 May 1962 the dosing being as set out in Table 4. After another four months the tumour exhibited distinct regression and its site was now occupied by gelatinous translucent tissue pervaded by dilated vessels. Appearances of this type may be regarded as a radiation reaction to be expected from the doses in question. The patient was seen in August 1963 when the translucent tissue had disappeared. No tumour was evident.

It may just be mentioned that a patient with a centrally located malignant melanoma in the remaining eye (the other eye had been traumatically injured at work) has been treated in the same manner as in Case 4 without showing any signs of recurrence during the year that has elapsed.

### Conclusions

It is apparent from these case reports that the modified  $^{60}\text{Co}$  applicator induces retrogression and even disappearance of the malignant tissue. One of the cases has been followed for 3½ months and another for approximately 20 months. On account of the small number of cases treated, and the limited period they have been observed, it would be unwise to draw any conclusions regarding the effectiveness of the treatment. Yet, with due consideration to the fact that it embodies the same fundamental principles as STALLARD'S  $^{60}\text{Co}$  applicators, the method can be hoped to yield no less favourable results. The method possesses some advantages over STALLARD'S technique — predominantly in offering superior application accuracy and shorter anaesthesia — and there would appear to be some justification in recommending it as a complement to other procedures used in the treatment of retinoblastoma.

### SUMMARY

A modified  $^{60}\text{Co}$  applicator embodying the same fundamental principles as the  $^{60}\text{Co}$  Stallard applicators for the treatment of retinoblastomata is described. Five cases are reported.

### ZUSAMMENFASSUNG

Ein modifizierter  $^{60}\text{Co}$  Applikator der nach denselben Prinzipien wie der Stallard  $^{60}\text{Co}$  Applikator gebaut ist, wurde für die Behandlung von Retinoblastomen angewendet. Fünf Fälle werden beschrieben.

### RÉSUMÉ

Les auteurs décrivent une modification de l'applicateur de  $^{60}\text{Co}$  de Stallard comportant les mêmes principes fondamentaux pour le traitement du rétinoblastome. Présentation de cinq cas.

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## WHOLE BODY AUTORADIOGRAPHIC STUDIES OF THE DISTRIBUTION OF SULPHUR 35 LABELLED MUSTARD GAS IN MICE

by

C. J. CLIFORDSON H. KRISTOFFERSSON B. SORBO and S. ULLBERG

Extensive studies of the biochemical and pathologic effects of mustard gas ( $\beta\beta$  dichlorodiethyl sulphide) were carried out both in the USA (see e.g. GILMAN & CATFELL 1948) and in England (see Biochemical Reactions of Chemical Warfare Agents 1948) during and after the second world war, and the essential action of this agent on biologically important compounds is now known. It has thus been found to react with purines, imidazoles, pyrimidines (WHELFER, MORROW & SHIPPER 1955), proteins (see e.g. BOURNELL 1948) and nucleic acids (see e.g. BERENBLUM & SCHÖENTAL 1947, BROOKES & LAWLEY 1960) as well as enzymes (see e.g. NEEDHAM 1948).

Liquid mustard gas rapidly penetrates the human skin and reacts with various cell constituents to produce the well known changes of erythema, vesiculation or necrosis, depending on the dose applied. Rapid penetration of the skin also occurs in animals but the reaction is different from that in human subjects and the effect also varies in different animal species. It has

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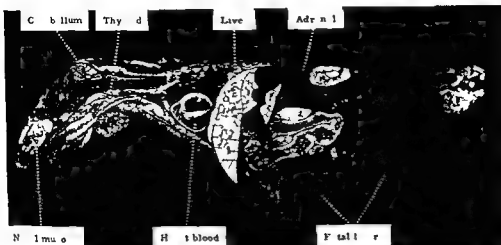


Fig 1 Distribut on of  $^{35}\text{S}$ -mustard gas in a pregnant mouse 5 min after intravenous injection. White areas correspond to high radioactivity fairly even distribut on throughout the body but an accumulaton is evident in the kidneys and liver and especially in the nasal region activity in the brain and fetuses

been demonstrated (AYELROD & HAMILTON 1947 CULLUMBINE 1954) that only about 12 per cent of the mustard gas penetrating the skin remains in situ the rest passes rapidly into the circulation

The fate of the mustard gas that is taken up by the blood is not known in detail The content of  $\beta\beta$  dichlorodiethyl sulphide or its degradation products has been determined in certain organs (BOURNELL COHEN et coll 1946 BOURNELL FRANCIS et coll 1946) but the overall distribution of the agent after systemic resorption is not known As mustard gas also has strong radio mimetic properties a study of its concentration in various parts of the body is of further interest The aim of the present investigation was to study the general distribution of  $^{35}\text{S}$  labelled  $\beta\beta$  dichlorodiethyl sulphide after its cutaneous and intravenous administration in mice

**Methods**  $^{35}\text{S}$  labelled  $\beta\beta$  dichlorodiethyl sulphide with a specific activity of 189 mCi/g was obtained from the Radiochemical Centre Amersham England The mustard gas was diluted with propylene glycol (10 mg dichlorodiethyl sulphide in 1.5 ml propylene glycol) Eighteen adult mice 15 males and 3 pregnant females weighing about 20 g were used for the experiments

The mustard gas was administered cutaneously to nine animals all males The animals were thoroughly clipped and shaved on a small area on the back and about 1 mg of the diluted mustard gas was applied to this area by means of a fine glass rod The diluted mustard gas in a dose of 0.20 ml per animal was administered intravenously into a tail vein in the remaining nine animals The animals were killed at various intervals by immersion in a mixture of solid



Fig. 2. Distribution of S-mustard gas in a pregnant mouse 1 hour after intravenous injection. Radioactivity now nearly completely excreted with exception of that in the nasal region, intestines, kidneys and bladder.

carbon dioxide and acetone ( $-78^{\circ}\text{C}$ ). The animals were sacrificed at the following times: cutaneous administration group 15 min, 1 hour, 4 hours, 1 day and 4 days after the administration, intravenous administration group 5 min, 15 min, 1 hour, 2 hours and 4 hours after the injection.

The frozen animals were sectioned and autoradiograms prepared according to the method developed by USTERGÅRD (1954, 1958) for autoradiography of small laboratory animals. Sagittal sections,  $20\ \mu$  thick, through the whole animal were made at different levels and the sections were then dehydrated at  $-10^{\circ}\text{C}$ . Gevart Dentus Rapid film was employed for all the autoradiograms (exposure time 32 days in all experiments).

## Results

*Intravenous administration.* The  $^{35}\text{S}$  mustard gas was rapidly taken up from the blood stream when administered intravenously. The radioactive isotope was fairly evenly distributed throughout the body with a significant accumulation appearing mainly in the liver and kidneys and especially in the nasal region at all times studied. The passage was apparently free to the brain and the isotope also rapidly passed the placenta.

A somewhat higher activity than in the blood was evident in a number of organs as early as 5 min after the injection of the compound (Fig. 1). The highest content of radioactivity was present in the nasal region followed by the kidneys, liver, intestines and salivary glands. The central nervous system showed evidence of a fairly high uptake with an even distribution of the activity but with some predominance in the granular layer of the cerebellum. A slight accumulation was also evident in the walls of larger arteries and in

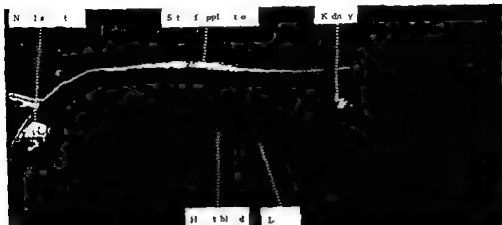


Fig 3 Distribution of  $^{35}\text{S}$  mustard gas in a mouse 15 min after administration to the skin. Rapid uptake in the nasal region.

the thyroid gland. The activity was very evenly distributed in the rest of the body and the lymph nodes: spleen, thymus, pancreas, suprarenals, pituitary gland and bone marrow all presented about the same activity as the skeletal muscles. The concentration of the isotope was low in the hard tissues, such as the bone and teeth, as well as in the cartilages.

The radioactivity disappeared quickly from most of the tissues except from the nasal region, the biliary ducts and urinary tract. The activity was very low in most tissues as early as 1 hour (see Fig 2), 4 hours after the administration of the radioactive mustard gas hardly any activity was detectable.

The fetuses had also taken up radioactivity, although the concentration in their tissues were lower than in those of the dam. The distribution pattern, however, was about the same in the fetus as in the dam.

In an attempt to determine whether the radioactivity in the nasal region was also present in the secretion, labelled mustard gas was given intravenously in two rats (dose 20 mg/kg bodyweight). The animals were then decapitated 15 min after injection and the nasal cavity was washed out with 10 ml saline. The washing solution was radioactive but its total activity corresponded only to 0.01 and 0.025 per cent respectively, of the dose injected in each animal. These figures appeared to be low when compared to the relatively high activity localized to the nasal regions in the autoradiograms, but this may have been due to difficulties in removing the nasal secretion by the washing procedure used.

*Cutaneous administration.* The  $^{35}\text{S}$  mustard gas applied to the skin was rapidly absorbed and as early as 15 min after the administration activity was found in various body tissues and organs of the animals (Fig 3). The distribution

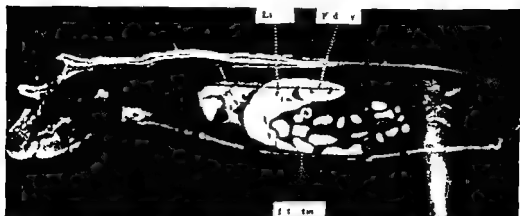


Fig. 4. Distribution of  $^{35}\text{S}$ -mustard gas in a mouse 4 hours after administration to  $\text{h.n.}$  Marked accumulation present in the kidney, liver and intestines.

pattern was essentially the same as that obtained after the intravenous administration of the compound. Thus, even in these animals the highest concentration was present in the excretory organs.

The high activity evident in the blood after the intravenous injection of the labelled compound was never encountered after its cutaneous application. On the other hand, it was found that significant amounts of the isotope remained in the body for a much longer time after cutaneous than after intravenous administration (see Figs 4 and 5). This was probably due to a slow continuous uptake of mustard gas or its degradation products from the skin. Thus, even 1 day after administration there was still a considerable amount of activity in the nasal region as well as in the intestines and bladder (Fig. 5), and the skin at the site of the application also retained a fair amount of the isotope.

### Discussion

The results of the present investigation are largely in agreement with those of BOURSVELL *et al.* (1946) who measured the  $^{35}\text{S}$  activity in various dissected organs of rabbits, after the intravenous administration of labelled mustard gas. These authors, however, reported a comparatively high activity in the lungs, the activity being of the same magnitude as that present in the liver. This is in contrast to the fairly low activity apparent in the lungs in the present study. It is of interest in this connection to note that DAVISON *et al.* (1961) reported only traces of radioactivity in the expired air of rats that had been given radioactive sulphur mustard gas. On the other hand, a comparatively high activity was found in the central nervous system in the present investigation, whereas BOURSVELL *et al.* measured only a fairly low activity in the brain in their experiments. This divergence in results may be due to the different techniques used and possibly also to species differences.

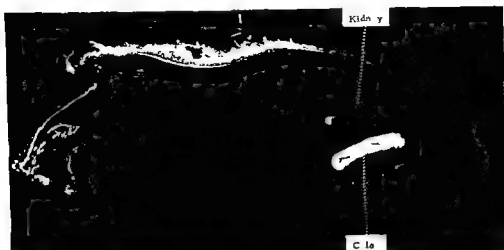


Fig 5 Distribution of  $^{35}$ S mustard gas in a mouse 4 days after administration to the skin. Some radioactivity still remains at the site of application

Since the whole body autoradiography method used allows rapid screening of almost all body tissues, accumulation of the radioisotope may be observed also at unexpected sites in the body. Thus, the high content present in the nasal region would probably have escaped detection if measurements had been made only on dissected tissues.

The radioactivity observed in the various organs and tissues in this study must be present as degradation products of the mustard gas and not as the parent compound itself (see e.g. BOURSNELL et coll 1946 and BOURSNELL 1948) as sulphur mustard gas is rapidly converted *in vivo* to degradation compounds of which thiodiglycol bis  $\beta$  chloroethyl sulphone and the conjugate with glutathione are the most important (DAVISON et coll 1961). It would have been of interest to identify these metabolites in the different tissues but this was beyond the limits of the present investigation.

### SUMMARY

$^{35}$ S labelled sulphur mustard gas was applied to the skin of mice and also given by intravenous injection; the distribution of the radioactivity being followed by whole body autoradiography. A high uptake was found in the kidneys and liver; the nasal region rapidly accumulated a high activity and considerable activity was also evident in the central nervous system. Some experiments in pregnant animals demonstrated a passage of radioactivity to the fetuses.

### ZUSAMMENFASSUNG

Schwefelgas, das mit  $^{35}$ S markiert war, wurde auf die Haut von Mäusen aufgestrichen und ebenfalls intravenös eingespritzt. Die Verteilung der radioaktiven Substanz wurde mittels Autoradiographie des ganzen Körpers studiert. Die Hauptaufspeicherung fand sich in den Nieren und der Leber; die Nasenregion zeigte bald eine rasch steigende Aktivität und beträchtliche Aktivität wurde auch im Zentralnervensystem gefunden. Versuche an schwangeren Tieren zeigten einen Übergang der Aktivität in die Embryonen.

## RÉSUMÉ

Les auteurs ont appliqué sur la peau et aussi administré par voie intraveineuse à des souris une yperite soufrée marquée au  $^{35}\text{S}$  et ont étudié par autoradiographie de tout le corps la distribution de la radioactivité. Ils ont constaté une fixation élevée dans les reins et le foie, la région navale fixe rapidement une activité élevée ainsi que le système nerveux central. Certaines expériences sur des animaux gravides ont montré un passage de la radioactivité dans les foetus.

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## INVESTIGATION OF A RADIOACTIVE DRUG (TRA 119) WITH SPECIAL REFERENCE TO AUTORADIOGRAPHIC AND RELATED STUDIES

by

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An attempt is being made by a team at Addenbrooke's Hospital Cambridge to develop a radioactive drug for the purpose of selective internal therapeutic irradiation in the treatment of patients with cancer. This approach is based on the assumption that sufficiently large biochemical differences exist between malignant cells and normal cells to make it possible to devise organic compounds which are concentrated or absorbed to some extent selectively by the cells of certain malignant tumours and carry incorporated radioactive atoms with high specific activity. Despite the great difficulties the possibility may be envisaged that a suitable radioactive drug could be curative since ionizing radiations are the only agents apart from surgery which as yet have cured substantial numbers of patients with cancer.

Tritium appears to be the most promising radioactive isotope for this application. Most of our investigations have concerned tritiated derivatives of 2-methyl-1,4-naphthoquinol bis (disodium phosphate) — Synkavit (Roche Products) our compound I. This compound, which has been investigated since 1946 as a

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therapeutic radiosensitizer was found unexpectedly to concentrate to some extent selectively in the malignant cells of some human and animal tumours (MITCHELL 1960). Studies of the distribution and selective concentration of compound I in the tumour and other tissues have been made, using the methods of fluorescence with Wood's light (MITCHELL 1949, 1953) and radioactive labelling with  $^{14}\text{C}$ ,  $^{81}\text{Br}$  and  $^{125}\text{I}$  (MARRIAN and MAXWELL, 1956 a and b, MAXWELL 1954, 1955) and with tritium (see MARRIAN 1957).

We have investigated the use of tritiated compound I in the treatment of patients with advanced malignant disease since February 1959. A number of accounts of various aspects of the laboratory and clinical investigations have been published (HORWITZ et coll. 1959, MARRIAN et coll. 1961, SIMON, REES 1961, MITCHELL 1961, 1962, CHIPPERFIELD and MARRIAN 1962). Information of great value from the point of view of the clinical applications in man was obtained in studies of the treatment of spontaneous malignant tumours and leukaemias in rats and dogs (SILVER et coll. 1962). It is of interest that preparations of tritiated compound I (TRA 72) produced mutations in the cruciferous plant *Arabidopsis thaliana*, similar to those produced by roentgen rays (McKELVIE 1962).

In the attempts to treat patients the preparations of tritiated compound I have been administered by some form of intra-arterial injection whenever possible otherwise by intravenous injection. In the treatment of the first 27 patients we used material tritiated by the Witzbach exchange method but this contained incorporated tritium at only relatively low levels of specific activity together with varying amounts of tritiated water.

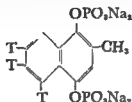
Then one of us (DHM) devised a method of tritiation which made it possible to obtain reliable preparations of the compound containing approximately one atom of tritium per molecule with the tritium firmly bound. This compound 2-methyl-6-tritio-1-4-naphthaquinol bis-(disodium phosphate) was prepared in collaboration with Roche Products, Welwyn Garden City and the Radiochemical Centre, Amersham (ANDREWS et coll. 1962). The material used was prepared by the Radiochemical Centre, Amersham accordingly we have found it convenient to describe it by the code designation in the catalogue of the Radiochemical Centre TRA 72.

We have investigated TRA 72 in the treatment of 21 patients who were seriously ill with advanced recurrent radioresistant or refractory malignant disease. Temporary improvement assessed on the basis of observation of some form of definite objective improvement and/or striking relief of pain as indicated by a great reduction of the analgesics required in particular discontinuance of the need for morphine was observed in 5 of these 21 cases. There was probably some improvement attributable to the treatment in a further 4 cases. It appeared that under the conditions of this trial definite though small palliative effects were observed. It seemed likely that these were associated with the relatively low levels of radiation dose delivered by the radioactive drug.

Extensive measurements of the specific activity of tritium in biopsy and autopsy specimens provided evidence for some degree of selective concentration of the compound in certain human malignant tumours in relation to the bone marrow after both intra-arterial and intravenous administration. The specific activity of the specimens of tumour was almost invariably higher than that of specimens of bone marrow and of skeletal muscle often by a factor of 3 and sometimes by a factor of 6 to 7. The values of the specific activity observed were such that it appeared that at least three atoms of tritium per molecule of compound I are neces-

sary to make it possible to deliver doses of radiation within the therapeutic range to tumours with adequate uptake and a sufficiently high radiosensitivity

The required drug 2 methyl 5 6 7 tritio 1 4 naphthaquinol bis (disodium phosphate) has been prepared as a result of a collaborative effort by the Department of Radiotherapeutics University of Cambridge the Radiochemical Centre Amersham and Roche Products Welwyn Garden City (ANDREWS et coll 1962) Its formula is given below



The preparations used will be referred to as TRA 119 again following the code of the catalogue of the Radiochemical Centre

During the last year we have carried out clinical and laboratory investigations of TRA 119 both to study its therapeutic possibilities and to obtain information necessary for widening the scope of its application and for the further development of radioactive drugs generally So far TRA 119 has been used in the treatment of 33 patients with advanced and recurrent malignant disease when conventional methods of treatment were not likely to help

The main aim of this paper is to consider the evidence for selective concentration of TRA 119 in the malignant cells of some tumours after intravenous and intra arterial injection, and to try to relate the concentrations of tritium observed in the malignant cells and normal cells to the therapeutic effects on the basis of some form of dosimetry

As with TRA 72 many measurements have been made of the specific activity of specimens of tumours and normal tissues obtained by biopsy surgery and autopsy after the administration of TRA 119 Following usual procedures, these macroscopic average values of the specific activity can be utilized for approximate calculation of the average doses of radiation delivered, on the basis of a number of assumptions of which the most important is that the radioactive material is uniformly distributed However the distribution of tritium is almost invariably non uniform both within the cells and in the tissues Accordingly the calculated values of the macroscopic average doses although of some interest cannot be expected to give reliable or detailed information concerning the effective doses of radiation delivered in many tissues and especially in the case of malignant tumours where a variable and often substantial proportion of the volume of tissue is occupied by stroma — quite apart from the variability of the malignant cells themselves

The use of a radioactive drug makes it necessary to study radiation dosimetry at the microscopic level and to try to evaluate the cell dose with the appropriate time factors For this purpose, autoradiographic studies have been carried out as an essential part of the investigation of TRA 119 So far it has not been possible to use these autoradiographs for quantitative cell dosimetry However

Table 1

*Cases treated by means of TRA 119 between 7.3.1962 and 17.12.1962 (all cases confirmed by histological examination)*

Diagnosis	Number of cases		
	Total	Intra-arterial route	Intra-venous route
Carcinoma of gastro-intestinal tract (stomach, caecum, colon and rectum) adenocarcinoma recurrent and advanced	7	4	3
Advanced cerebral glioma in conjunction with surgery	8	8	0
Carcinoma mammae advanced and recurrent	3	0	3
Malignant melanoma of skin recurrent	3	1	2
Carcinoma of skin advanced and recurrent	2	1	1
Carcinoma of head of pancreas with extensive metastases	1	0	2
Metastases in liver — adenocarcinoma but no primary found	1	1	1
Hodgkin's disease advanced with generalised pruritus	1	0	1
Mycosis fungoides advanced after much radiotherapy	1	0	1
Neuroblastoma advanced	1	0	1
Seminoma of testis advanced and recurrent	1	0	1
Carcinoma of Fallian tube metastases after surgery and radiotherapy	1	0	1
Secondary carcinoma in R femur primary uncertain	1	1	0
Reticulum cell sarcoma of bone with extensive metastases	1	0	1
Total numbers	33	1	18

the qualitative and semi quantitative autoradiographic findings taken in conjunction with the measured values of the macroscopic specific activity appear to give useful information.

*Some clinical aspects* The selection of patients for the investigation of the therapeutic possibilities of TRA 119 presents many problems. So far we have felt compelled to follow the general principles of selection of patients which we used for the studies of TRA 72 (see MARRIAN, MARSHALL and MITCHELL 1961, p. 286). The cases which have been treated may be classified in the following main groups:

1 Late cases, where no form of conventional treatment is likely to be able to offer further help i.e. with advanced, recurrent radioresistant and refractory tumours.

2 Earlier, in the sense of somewhat less advanced, but otherwise untreatable cases.

3 Advanced cases of highly radiosensitive malignant tumours and allied diseases.

The cases treated by means of TRA 119 between 7.3.1962 and 17.12.1962 are summarised in Table 1. The previous studies with TRA 72 suggested that particular attention should be paid to adenocarcinoma of the gastrointestinal

tract malignant melanoma, advanced carcinoma of the skin and the highly radiosensitive malignant diseases. Of particular interest is the study of advanced cerebral glioma which is being carried out in collaboration with Mr Walpole Lewin and Dr T. D. Hawkins and will be the subject of a separate report.

In addition to the cases listed in Table 1, so far 4 cases of carcinoma of the bronchus have been investigated by means of pre-operative injections (three intravenously and one into the pulmonary artery) with subtherapeutic doses of TRA 119.

In Table 2 is summarised some more detailed information about 6 cases, which were selected because of the type of disease and the availability of biopsy specimens for which autoradiographs showed uptake of TRA 119 into tumour cells and in which measurements of the specific activity have been made.

The results of measurements of the specific activity of autopsy specimens in one of the cases 14 days after intra-arterial injection of the dose of 10.8 curies of TRA 119 which is one of the largest single doses administered so far, are recorded in Table 3. In this case intra-arterial injection was made through a catheter into the external carotid artery which had been exposed surgically.

Evidence will be discussed for two other cases in which apparently satisfactory autoradiographs showed no evidence of uptake into the tumour cells. Further, it is of interest that there were 6 cases in which single intravenous doses of between 9.6 and 10.9 curies of TRA 119 were administered; only one of these—a case of carcinoma of the head of the pancreas with extensive metastases in bones—showed evidence of a serious fall in the level of blood platelets with petechial haemorrhages. This example appears to have been the only serious toxic effect attributable to TRA 119 in this series of 33 cases. In a few cases where the amount of TRA 119 given corresponded to more than 75 mg of compound vasomotor reactions were observed but these were never serious.

It is of course too early to draw any general conclusions about the possible therapeutic value of TRA 119 and great caution is necessary. (For a discussion of the methods of assessment see MARRIAN, MARSHALL and MITCHELL 1961.) At present, it can be reported that there was useful relief of pain in 6 out of 9 cases in which pain was a serious problem and in one case of Hodgkin's disease generalised pruritus was relieved after a single intravenous dose of 2.9 curies. Moreover, in Case 52 (see Table 2) there appeared to be delayed retrogression of metastatic nodules of melanoma after three intra-arterial injections of TRA 119.

The procedures for intra-arterial injection of TRA 119 and the methods used have been described (HORWITZ et al. 1959; GREGG 1960; MARRIAN, MARSHALL and MITCHELL 1961, p. 287). In general a preliminary arteriogram is carried out. Tolazoline (Priscol) has been used in many cases before the intra-arterial injection of TRA 119. Although the general policy has been to give a single intra-arterial injection of TRA 119, an attempt is being made in some cases to repeat the intra-arterial injection after an interval of between 10

Table 2

*Details of selected cases treated by TRA 119 (\* indicates that autoradiographs of part of the specimen*

Case No	Disease and previous treatment	Age in years sex and height	Route of injection and date	Amount of TRA 119 injected	
				l. r. cm	mg
49	Metastases in anterior abdominal wall Ca rectum adenocarcinoma abdominal perineal resection 11.59	66 M 51 kg	IV 7.3.62	1.4	8
			IV 4.5.62	1.3	16.5
			IV 29.5.62	1	16.5
			Died 11.10.62		
57	Metastases of malignant melanoma of skin multiple recurrent nodules of R leg below knee mole removed 5.8.53 re-excision of primary site and Block dissection of inguinal nodes (not involved) 10.9.53 excision of recurrent nodules 18.4.59 and in September 1960	46 F 55 kg	IV 19.4.62	1	7.5
			IV 16.62	4.2	21
			IV 4.7.62	9.8	74
66	Fungating metastases of anterior abdominal wall advanced recurrent Ca caecum — adenocarcinoma hemicolectomy and side to-side anastomosis 18.9.62 laparotomy and excision of recurrent tumour March 1962 post-operative Indoxan	37 F 54 kg	IV 30.7.62	5.2	34.5
			IV 17.8.62	9.9	69

are shown in the figures)

Specimen and time after injection	Specific activity of specimen ( $\mu\text{Ci}$ per gram of wet tissue)		Clinical response and other information
	Tumour	Other specimens	
Biopsy 30 min	*28.3 ( $\pm 1$ )	Adjacent muscle 15.5 ( $\pm 1$ )	Slowly growing well-differentiated tumour with grossly fibrotic stroma Relief of pain after first injection no objective evidence of tumour inhibition.
—			
Autopsy	*25.8 ( $\pm 2$ )		
Biopsy 30 min	74.3 ( $\pm 13$ )	Muscle 27.8 ( $\pm 6$ )	Good general condition no evidence of extension of the tumour outside the R leg below the knee sternal marrow normal 28.6.62
30 min		Peripheral blood 72 $\pm 1$	Compression of vessels and withdrawal of effluent blood from limb
—			Appeared to have late retrogression of nodules 16.11.62 including new nodules which had developed since injections
Biopsy nodule near ankle 41 min	*84.2 ( $\pm 2$ )		
Nodule near knee 46 min	80.4 $\pm 2$		
1 hour		Peripheral blood 78 ( $\pm 4$ )	
Biopsy 30 min	95 ( $\pm 34$ )		Very ill and grossly anaemic requiring transfusion no evidence of tumour inhibition
30 min	300 ( $\pm 1$ )		
7 days	8.8 ( $\pm 3.5$ )		Med 15.9.62

Table 2 (cont.)

Case No	Disease and previous treatment	Age in years sex and weight	Route of injection and date	Amount of TRA 119 injected	
				Curies	mg
71	Extensive recurrent squamous carcinoma of L. pinna involving side of head and neck original excision 11.1.62 further surgery on 22.2.62 and 4.4.62 and radical Ca 131 teletherapy 7.5.62 to 8.6.62	66 M 47 kg	IA 6.9.62	108	14
			Died 20.9.62		
80	Recurrent nodules on chest wall spheroidal-celled carcinoma and axillary nodes Ca mammae R stage III recurrences after roentgen therapy 29.5.61—16.6.61 simple mastectomy 12.1.62 and local roentgen therapy 16.4.62 and 14.6.62 no response to Durabolin	59 F 101 kg	IA 9.11.62	101	73.5
8f	Recurrent mass in L. ischio-rectal fossa and perineum Ca rectum adenocarcinoma abdomino-perineal excision 16.5.62	53 F 67.5 kg	IA 4.12.62	9.7	57.4

days and 4 weeks. For both intravenous and intra-arterial routes of administration, it is considered important to inject the TRA 119 as rapidly as possible in order to minimise its reaction with SH compounds in the blood and to make certain that as high a proportion as possible reaches the tumour cells.

*Preparations of TRA 119 used.* The compound 2-methyl-5,6,7-tritio-1,4-naphthaquinol bis (disodium phosphate) corresponds to a specific activity of 87.3 curies per mM, accordingly 1 curie is contained in 4.88 mg of compound.

The TRA 119 is prepared by the Radiochemical Centre, Amersham in batches which usually contain between 10 and 30 curies. The specific activity of the different batches has varied considerably and was usually between 50 and 80 curies per mM.

It is interesting that the use of batch No. III which had the theoretical value of 87 curies per mM corresponding to 3 atoms of tritium per molecule gave high values of the uptake into

Table 2 (cont.)

Specimen and time after injection	Specific activity of specimen ( $\mu\text{C/g}$ gram of wet tissue)		Clinical response and other information
	Tumour	Other specimens	
Biopsy 30 min	Anterior part 8990 ( $\pm 27$ )	Peripheral blood 399 ( $\pm 17$ )	Deteriorated and died with severe bronchopneumonia at autopsy (Dr R W Answorth) carcinoma cells show severe degenerative changes with conspicuous vacuolation of their cytoplasm
3 / hours	Anterior part 378 ( $\pm 26$ ) *Posterior part 1815 ( $\pm 38$ )	(See Table 3)	
Autopsy	403 ( $\pm 5^*$ )		
Biopsy skin nodule 35 min	*1025 ( $\pm 1$ )		Complete relief of pain but objectively no improvement
Biopsy Perineal recurrence 30 min	*28 ( $\pm 4$ )		Pain relieved temporarily but no objective improvement

specimens of tumour per curie injected in a recurrent cerebral glioma (Case 50) and a metastatic nodule of malignant melanoma (Case 52 first injection) though there was not a high uptake in a biopsy specimen of primary carcinoma of the rectum (Case 51). There appears to be some association between the values of the specific activity of the preparation of TRA 119 used and of the uptake into biopsy specimens of tumour defined in terms of microcuries per gram per curie injected but there is obviously considerable variation between the uptake of the tumours in different patients. The highest values of the uptake observed so far were in Case 71 (see Table 2) after intra arterial injection of a preparation (batch No 20) of specific activity 62 curies per mM. The limited evidence available confirms that the uptake into tumour biopsy specimens is usually higher with the preparations of TRA 119 of specific activity in the range between 60–87 curies per mM than with preparations of TRA 72 of a specific activity of between 16 and 29 curies per mM.

The solutions of TRA 119 are sterilised by filtration into sterile rubber-capped bottles. Chlorocresol is added as a bacteriostatic to give a concentration of 0.2%. The solutions are



Table 3

*Specific activity of autopsy specimens (Case No 71) 14 days after intra arterial injection of 10.8 curies of TRA 119 into the exposed left external carotid artery through a catheter and after arteriography and a further injection of Prisol (body weight 47 kilograms)*

Tissue	$\mu\text{Ci}$ per gram of wet tissue	Tissue	$\mu\text{Ci}$ per gram of wet tissue
Tumour	$40.25 \pm 5$	Skeletal muscle	$7.5 \pm 5$
Bone marrow	$10.2 \pm 4$	Cardiac muscle	$13.7 \pm 1$
Kidney	$42.1 \pm 1$	Lung	$11.2 \pm 1$
Small intestine	$20.1 \pm 2$	Testis	$21.7 \pm 5$
Spleen	$13.0 \pm 3$	Brain—right temporal lobe	$10.9 \pm 2$
Liver	$15.9 \pm 2$	Brain—left temporal lobe	$10.4 \pm 4$
Pancreas	$13.7 \pm 1.7$		$11.4 \pm 5$

frozen immediately delivered in containers surrounded by solid  $\text{CO}_2$  and kept at  $-78^\circ\text{C}$  surrounded by solid  $\text{CO}_2$  in a Dewar vessel in a deep freeze at ambient temperature about  $-20^\circ\text{C}$ .

Each batch of TRA 119 is tested biologically before the clinical use by the two methods  
1 To exclude the possibility of acute toxicity by intravenous injection into a rabbit in doses corresponding at first to 11 curies per 70 kg of body weight and later to 22 curies per 70 kg. No acute toxic effects have ever been encountered. The rabbits are being kept for the rest of their life span under observation with regular blood counts for which we are indebted to Mr R. Flemans. Full autopsy studies are planned.

2 Studies on tissue cultures mainly of HeLa cells, to check sterility and to demonstrate the uptake of TRA 119 into the tumour cells under standard conditions by means of autoradiography (see SIMON REUSS 1961).

The difficulties raised by the decomposition of TRA 119 in aqueous solution as a result of auto-irradiation has been overcome to a large extent by the low temperature storage. Nevertheless, despite this deterioration of the material occurs in the frozen solution. The problems of radiation stability and chemical purity are being investigated by our colleagues at the Radio-chemical Centre, Amersham from the biological point of view by means of the autoradiographic studies on tissue cultures. Mrs Simon Reuss has found that many batches show no substantial decrease in the labelling of the tumour cells with only a little increase in background after two weeks though some batches deteriorate more quickly. Accordingly it is considered that good batches can be used for up to two weeks and perhaps even up to three weeks. An account of these studies will be published separately.

*Measurement of specific activity of specimens of tissue* For routine assay of tritium the tritiated water obtained by combustion of specimens of tissue of weight 10 to 40 mg has been counted in a Nuclear Enterprises NE 8301 liquid scintillation counter using either N1 213 scintillator or SP2 (Nash and Thompson Ltd Chessington Surrey) (See MARRIAN, MARSHALL and MITCHELL 1961 p 282). The efficiency of the counter was checked regularly by counting a sample of tritiated water of known specific activity. At first the weighed specimen of tissue was sealed into a hard glass tube (M J V combustion tubing) together with copper oxide and reduced copper and heated at  $650^\circ\text{C}$  for 6 hours (JACOBSON et al 1960) the water formed was sublimed in vacuo into a vial and kept for counting. More recently the tissues have been burned in a flask of oxygen (SCHONICER 1955-1956) containing a known volume of water as scavenger. Aliquots of water were then counted as before.

*Histologic and autoradiographic techniques* At first the specimens of tissue were fixed in Susa and the sections stained with Ehrlich's haematoxylin (see Fig 1). It appeared that diffusion

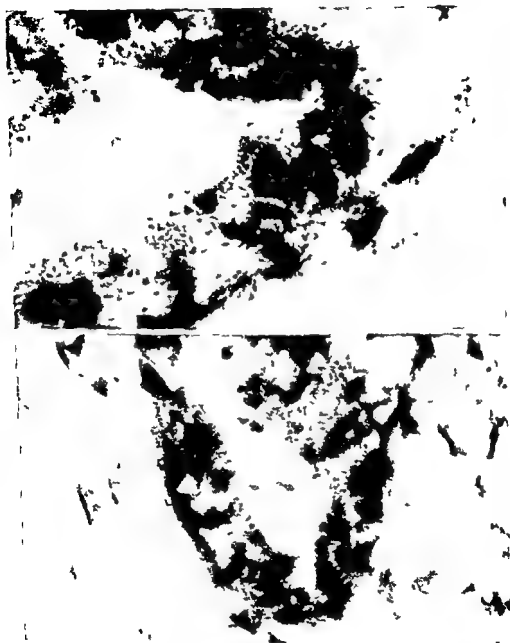


Fig 1 Case 49 Sections of metastases of adenocarcinoma of rectum. Autoradiographs of biopsy specimens upper view  $\times 1750$  lower view  $\times 1050$

of the radioactive material in the specimens of tumour was a problem and it became necessary to use a freeze-drying preparation of the tissues. In general standard procedures have been followed. The specimens of tissue were frozen as quickly as possible after removal by plunging into liquid isopentane cooled with liquid nitrogen. Vacuum dehydration of fragments of dimensions of about 5 mm was carried out at temperatures between  $-30$  and  $-50$  °C for 5 days and was followed by embedding in degassed paraffin wax under vacuum. Sections were cut at thickness  $5\mu$  selected as corresponding to a layer of infinite thickness in relation to the range of the beta particles of tritium (see ROBERTSON and HUGHES 1959). Autoradiographs were prepared with  $C_{11}$  liquid emulsion (Ilford) with exposure times at 3 °C between 12 hours and 10 days according to the specific activity. ID 19b developer (Ilford) for 10 minutes then fixation, washing in distilled water and immersion in 70 per cent alcohol at 3 °C and Feulgen staining.

### Dosimetric considerations

As a preliminary to consideration of the results of measurement of the specific activity of the specimens of tissues and of the evidence provided by the autoradiographs it is necessary to summarise the relevant physical properties of tritium and the calculations of the dose of radiation delivered (see MARRIAN, MARSHALL and MITCHELL 1961, MITCHELL 1962).

The best value of the mean energy of the beta particles of tritium is  $5.73 \pm 0.03$  keV, corresponding to the half life  $12.43 \pm 0.04$  years (PILLINGER, HENTGES and BLAIR 1961).

The range in unit density tissue corresponding to the mean energy of the beta particles of tritium is approximately  $1\mu$ . The maximum energy of the beta particles is  $18.7 \pm 0.1$  keV, so that the corresponding maximum range is approximately  $6\mu$ .

Calculations of the radiation dose rates and isodose curves about a point source of tritium in unit density tissue have been published (ROBERTSON and HUGHES 1959, ROBERTSON, BOND and CROWLITZ 1959, KUKAFL 1962). Radiation dose calculations in cells containing intranuclear tritium have been made (GOODHEART 1961, KUKAFL 1962).

The linear energy transfer for the beta particles of mean energy has the value of ca. 4 keV per  $\mu$ , near the end of the track, the value of the linear energy rises to about 11 keV per  $\mu$ .

On the basis of a value of the mean energy of the beta particles of tritium of 5.73 keV and with the assumption of uniform distribution of the radioactive material, approximate calculations have been made of the macroscopic average values of the dose delivered by tritium from the point of view of its therapeutic applications. 1 mCi tritium per gram of tissue delivers a dose of 293 rad in 24 hours. Other results are given in Table 4 (see also MITCHELL 1962). A brief discussion is necessary to consider the implications of the numerical values.

The limited evidence available, mainly from the studies of TRA 72, concerning the values of the biologic half life of the tritium in tumours and normal tissues has been discussed elsewhere (see MARRIAN, MARSHALL and MITCHELL 1961). It appears that the value of the mean biologic half life (BHL) is in the

Table 4

*Dosimetry of tritium in therapeutic applications (approximate dose delivered by one curie of tritium administered to a 70 kg patient)*

Biologic half life	3 days	6 days	9 days	12 days	13 days
Calculated value of total dose delivered	18.12 rad	36.2 rad	54.4 rad	72.5 rad	185 rad
Mean life	4.33 days	8.66 days	13.0 days	17.3 days	18.8 days
Time factor assumed for calculation of the equivalent single acute dose (see Mitchell 1960 p 234)	2.22	2.54	2.64	2.69	2.71
Approximate equivalent single dose delivered at high dose rate	8.2 say 8 rad	14.3 say 14 rad	20.6 say 21 rad	26.9 say 27 rad	29.0 29 rad
Approximate biologically equivalent single dose of Co gamma radiation (R.B.E. = 1.7)	14 r	24 r	35 r	46 r	50 r

These calculations assume uniform distribution of the tritium throughout the body and give the approximate dose for different values of the biologic half life

region of 13 days for a number of different tumours though values as low as about 3 to 4 days have been observed, for case No. 66 treated with TRA 119 the findings are consistent with a value of 1.4 days. The rapid initial loss of radioactivity from at least some tumours, with a half life of about 8 min in one case needs further investigation. The possibility of an additional very long half life must be envisaged for some tumours. It is likely that the values of the main biologic half life for many normal tissues including bone marrow, are in the region of 3 to 6 days. The apparently higher value in the region of 11 to 12 days found for the small intestine in the autopsy studies also needs further investigation.

The best estimate of the relevant value of the relative biologic effectiveness (R.B.F.) of the tritium beta particles of TRA 119 in relation to Co gamma radiation is 1.7. This value must be regarded as provisional and needs direct experimental investigation from the point of view of therapeutic applications. The possibility may be envisaged of somewhat different values of the R.B.E. for TRA 119, tritiated water and tritiated thymidine.

It can be deduced from Table 4 as a first approximation that the maximum single amount of TRA 119 which can be administered with safety to the whole body in a patient of weight 70 kg is approximately 11 curies. The safety of this amount has been confirmed for patients without serious bone marrow damage. It is likely that the calculation involves a safety factor on account of the non-uniformity of the macroscopic distribution of the tritium, in addition to the

effects of non uniform distribution of the compound within the cells. The size of the safety factor is not yet known but it is necessary to be cautious about this particularly because of the possibility of late effects of the irradiation on the kidney during excretion.

In these calculations account must be taken of the differential absorption ratio (DAR) which is defined as the ratio of the observed radioactivity per gram of tissue to the total injected radioactivity per gram of body weight (cf KENNY, MARINELLI and WOODWARD 1941). Again it is to be noted that the DAR refers to the macroscopic average value.

For the administration of 11 curies in a patient of body weight 70 kg the calculations on the basis of Table 4 lead to the following approximate values of the biologically equivalent single dose of  $^{60}\text{Co}$  gamma radiation

for bone marrow with BHI 4 days 190 r

for small intestine with assumed BHI 11.5 days 480 r

for kidney with BHI 6 days and assumed DAR 2 530 r

for tumour with BHI 3 days 150 r, and for BHL 13 days 50 r

In these calculations, the limiting factor was taken to be the threshold for acute radiation effects on the small intestine, it was noted that the threshold dose for the gastro intestinal form of the acute radiation syndrome in man after total body irradiation is given as 500 r (GERSTER 1958). In fact, after intravenous injection of 9.6 to 10.9 curies in patients of different body weights only slight nausea was observed in one case. Further the absence of appreciable haematologic changes in patients with essentially normal bone marrow, together with the crude calculations of the dose received by the kidney, suggest that the safety factor may prove to be about 50 per cent.

The calculated doses for tumour are consistent with the striking palliative effects observed after intravenous injection of TRA 119 in some advanced cases of certain highly radiosensitive diseases e.g. Hodgkin's disease, testicular seminoma. However to obtain useful therapeutic effects with most malignant tumours, a high DAR is essential. It can be assumed that with a single dose of gamma radiation, a minimum tumour dose of about 2250 r is required to cure a squamous carcinoma of a diameter of about 1 cm. Accordingly, the DAR required must be at least about 4 to 15 depending on the BHL, in fact higher values are necessary for more extensive tumours. The simplest method of attaining these high values of the DAR appears to be by means of intra arterial injection of the TRA 119, with draining off of the returning venous blood whenever possible. With intra arterial injection, the total amount of TRA injected may be limited by the radiosensitivity of the normal tissues concerned, especially the gastro intestinal tract and probably also the brain. It seems likely that the time factors are such that radiosensitization by the compound is not important, although this possibility cannot be completely excluded.

These admittedly crude calculations are of some interest in that by this method it has been possible to reach a provisional working level of maximum

safe dosage of TRA 119 for administration to the whole body. However it must be emphasised that this level has been approached cautiously and empirically and that it may be possible to go to somewhat higher levels such as 16 curies per 70 kg of body weight, in patients with essentially normal bone marrow, when preparations of TRA 119 of the full theoretical specific activity 87 curies per mM become regularly available.

The next and apparently most difficult step is to relate the calculated macroscopic average doses to the biologically and therapeutically effective cell doses taking into account the distribution of the tritium of TRA 119 among the different cells and within the cells, together with the appropriate time factors.

As with all the previous therapeutic applications of the internal use of radioactive isotopes, this development is basically empirical but every effort must be made to establish some form of quantitative dosimetry.

### Discussion

Measurements of the specific activity of specimens of tumour and some other tissues are given in Table 2 for the 6 selected cases. Table 3 gives the measurements of the specific activity in one of these, Case 71, after intra arterial injection of 10.8 curies of TRA 119.

In Table 2 the specimens of tumour from parts of which autoradiographs are presented are indicated by asterisks. Representative autoradiographs for these specimens are shown in Figs 1 to 7. It is to be noted that the grains are in focus so that the cells are in general out of focus. For Case 49 the histologic appearance of part of the biopsy specimen is shown in Fig. 2a at low magnification to demonstrate the small proportion of the volume of the metastatic tumour mass occupied by tumour cells. In studies of the autoradiographs of these and other cases approximate estimates have been made of the proportion of tumour and stroma cells labelled and the mean grain count per labelled cell.

The first problem to be discussed is the assessment of the value of the D A R which is relevant to the production of therapeutic effects and to the estimation of the dose of radiation delivered. The calculated values of the macroscopic D A R for the different tumours are of particular interest and must be considered in relation to the mode of administration of the TRA 119 — whether intravenous or intra arterial — the proportion of the macroscopic specimen of tumour occupied by tumour cells as shown by histology and the distribution of the radioactive material both in the tumour and normal cells and within the tumour cells as shown by autoradiography.

For Case 66 of recurrent adenocarcinoma of the caecum the macroscopic D A R for the biopsy specimen taken at 30 min after intravenous injection of 9.8 curies of TRA 119, had the value 1.64 which must be regarded as significantly greater than unity. The histologic structure, as seen in the autoradio



Fig. 2 Same case as in fig. 1. Section of biopsy specimen (upper)  $\times 61$ .  
Autoradiograph of autopsy specimen (lower)  $\times 1,300$ .

graphs in Fig. 4 shows that there is only a very little stroma but that the specimen contains considerable acinar and intercellular spaces, in addition to the tumour cells. Measurements showed that about two thirds of the area of the sections was occupied by cells and about 60 % by tumour cells. Accordingly, it can be assumed that about 46 %, say 50 %, of the volume of this specimen was occupied by tumour cells. The autoradiographs show that almost all the tumour cells were labelled under the experimental conditions. Crude values for the mean grain counts per cell were about 16 for tumour cells and about 8 for stroma cells with wide variation among cells. It seems reasonable to conclude that the DAR for tumour cells i.e., in relation to the mean concentration of radioactivity average over the whole body had a value of about 3.3. This value will be considered again later in relation to the concentration of tritium within the tumour cells and the problem of cell dose. However,

it is of interest that in this case, the value of the D A R for the tumour cells is greater than unity after intravenous injection of TRA 119

For Case 49 of recurrent adenocarcinoma of the rectum the microscopic D A R for the biopsy specimen from the metastases in the anterior abdominal wall at 30 min after intravenous injection of 1.4 curies of TRA 119 had the value of 1.04, which is not significantly different from unity. However it is important to note that histology showed a very substantial proportion of the specimen to be occupied by fibrous stroma (Fig. 2). Measurements showed that only 7.6 % of the area of a section of the biopsy specimen was occupied by tumour including acinar spaces. The histologic structure (Fig. 2) suggests infiltration by the well differentiated adenocarcinoma in association with an extremely marked stroma reaction. Accordingly in this case spherical symmetry is not likely and it is best to assume that only about 8 % of the volume of the biopsy specimen was occupied by tumour including acinar spaces. The autoradiographs (Fig. 1) show a high degree of selective uptake of tritium in many of the tumour cells and apparently all the tumour cells at the growing point of the acinus shown, however there is only a low uptake in the stroma, both for the cells and for the matrix. Quantitatively the grain count per arbitrary unit area of section was approximately 1.09 for the tumour cells and approximately 0.047 for the stroma, the very low background count was neglected. About 65 % of the total radioactivity in the macroscopic specimen was concentrated in the tumour which occupied only about 8 % of the total volume so that the microscopic D A R for the tumour cells had a value of not less than about 8.

The autoradiographs of sections of specimens of the same metastases obtained at autopsy in Case 49 are shown in Fig. 2b. Even at 135 days after the last intravenous injection of 2.64 curies of TRA 119, some tritium still persisted in a few areas in degenerating remains of tumour cells; there was no labelling of the stroma cells. No labelling was seen in actively proliferating tumour cells. These findings suggest that there is a long biologic half life of the incorporated tritium for some of the tumour cells and that delayed degeneration of tumour cells is possible under some circumstances as a late result of the uptake of TRA 119. This matter needs further investigation.

For Case 80 of recurrent carcinoma mammae the macroscopic D A R for the biopsy specimen of a metastatic nodule in skin taken at 35 min after intravenous injection of 10.1 curies of TRA 119 had the value 1.03 which is, of course not significantly different from unity. The histologic examination and the autoradiograph (Fig. 6) showed the specimen to be largely occupied by tumour cells with relatively little stroma and few stroma cells. The autoradiograph shows the presence of tritium in most of the tumour cells but grain counts showed that about one third of the tumour cells had 3 grains or less per cell while the approximate mean grain count for the rest of the tumour cells was about 6 grains per cell with wide variation between cells. Almost all the



stroma cells seen contained either no grains or one grain per cell under the present experimental conditions. Accordingly there is no convincing evidence for a useful concentration of tritium in the tumour cells or for a value of the macroscopic D A R for the tumour cells substantially greater than unity in Case 80.

At this point mention may be made of two cases, in which apparently satisfactory autoradiographs of biopsy specimens showed no appreciable labelling of the neoplastic cells after intravenous injection of TRA 119. For one of these, Case 63 of advanced recurrent carcinoma mammae which had arisen during lactation, the specific activity of the preparations of TRA 119 used was low, viz. 40 and 42 curies per mM, however the failure of uptake may be attributable to the nature of the tumour since there was evidence of uptake into HeLa cells in tissue culture. In the other case, Case 72 of advanced mycosis fungoides after much external irradiation, the specific activity of the preparation of TRA 119 used was 62 curies per mM but this preparation was found to show negligible uptake into the HeLa cells on testing in tissue culture. Accordingly, at present it is not possible to draw any conclusions about the uptake of TRA 119 into the neoplastic cells in mycosis fungoides.

The evidence concerning the values of the D A R for the tumour in cases treated by intra-arterial administration of TRA 119 is of particular interest in relation to the possibility of treating patients with relatively localised but otherwise untreatable malignant disease.

A number of problems are raised by Case 52, of recurrent nodules of malignant melanoma, treated by means of three intra-arterial injections of TRA 119. The biopsy of a nodule of tumour taken at 30 min after the first intra-arterial injection of 1.5 curies of a preparation of TRA 119 of specific activity 87 curies per mM had a value of the macroscopic D A R of 2.72. The biopsy of adjacent muscle had a D A R of unity and peripheral blood 2.6. For the biopsy of another nodule of tumour taken at 41 min after the third intra-arterial injection of 9.8 curies of a preparation of TRA 119 of specific activity 56 curies per mM, the macroscopic D A R was only 0.47. The histologic and autoradiographic appearances of this specimen are characterised by patchy uptake of tritium, with many areas with little demonstrable uptake, but some areas such as those shown in Fig. 3, with considerable uptake into apparently all the tumour cells and little or no uptake into stroma cells. However, in some of the areas of considerable uptake into tumour cells, there is a rather high local background. Only a few of the tumour cells are pigmented. The histologic appearance of patchy uptake in the biopsy specimen after the third injection probably reflects a changing non-uniformity of the blood supply in these secondary nodules at different times. It is possible that the relatively low uptake expressed in terms of  $\mu\text{C}$  per gram of wet tissue per curie injected may be associated with a poor batch of TRA 119 of rather low specific activity, further, the two previous injections may have produced radiation effects. In any case, it is of

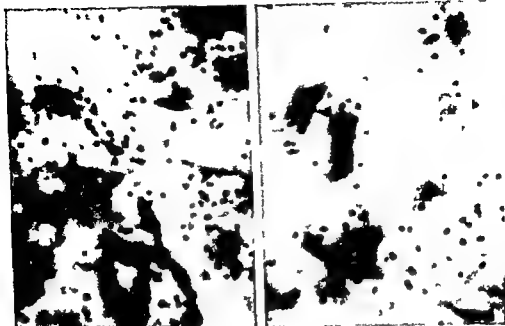


Fig 3 Case 59. Autoradiographs of section of metastatic nodule of malignant melanoma  $\times 1000$

great interest that in this patient there appeared to be late retrogression of the secondary nodules including retrogression of new nodules which had developed since the injections. This observation does not refer to two nodules which appeared to be growing and were treated with single doses of 1750 r of roentgen rays delivered to localised small fields of diameters 1.5 and 2.0 cm respectively. Although the late retrogression of the secondary nodules observed at 135 days after the last injection may be attributable to the treatment, it is difficult to be certain of this, because 'the behaviour of no other tumour is so unpredictable as that of melanoma and occasionally a melanoma which has already metastasized undergoes spontaneous retrogression (see WILLIAMS, 1968)'. (p. 908)

The highest values of the specific activity of biopsy specimens of tumour and of the corresponding macroscopic D.A.R. so far attained have been obtained in Case 71, of extensive recurrent squamous carcinoma of the pharynx and larynx. The patient was treated, after failure of surgery and radiotherapy, by intra-arterial injection of 10.8 curies of TRA 119 (of specific activity 600 Ci/g, 22.2 MBq/mg) through a catheter into the external carotid artery which had been exposed surgically. The arteriogram showed partial thrombosis of the external carotid artery but filling of the occipital branch, with increased vascularity and patchy blood supply to the region of the tumour after intra-arterial injection of

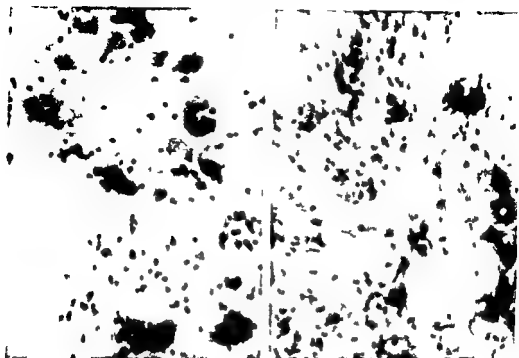


Fig 4 Case 66. Autoradiographs of section of metastasis of adenocarcinoma of caecum 1900

tolazoline (Priscol), which was used as a vasodilator before the injection of TRA 119. It must be concluded that in this case the blood flow through most of the tumour was unusually slow. The patient's general condition was poor. Unfortunately, at about 3 days after the intra arterial injection, he became confused, he then deteriorated and died with severe bronchopneumonia at 14 days after the injection. At autopsy, the histologic examination of the edge of the ulcer showed severe degenerative changes in the carcinoma cells; these changes are consistent with irradiation by the TRA 119 at a therapeutic level.

The value of the macroscopic D A R for a biopsy taken from the anterior part of the tumour at 30 min after the intra arterial injection of 10.8 curies of TRA 119 was 39. For further biopsies taken at 3 1/2 hours after the intra arterial injection, the D A R for a specimen from the anterior part of the tumour was only 1.64, while the D A R for a specimen from the posterior part of the tumour was 7.9. The autoradiographs for this latter specimen are shown in Fig 5. There is considerable variation in the histologic appearances especially with respect to differentiation of the squamous carcinoma cells, in different parts of the sections of this specimen. However, throughout the specimen there is heavy labelling of tumour cells and only slight labelling of stroma cells. Under the experimental conditions, the value of the mean grain count was about 35 per cell for the tumour cells and about 5 per cell for adjacent stroma cells.

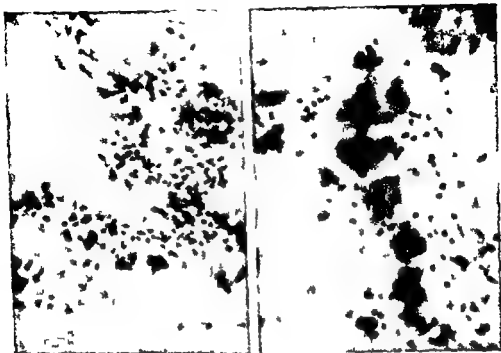


Fig 5 Case 71 Autoradiographs of section of recurrent squamous carcinoma of pinna  $\times 1900$

with wide variation among cells in both cases. The specimen consisted largely of tumour cells with relatively little stroma. Accordingly, for the biopsy specimen in question, the effective microscopic D.A.R. for the tumour cells had the value of at least 8. It is to be noted, however, that there were areas of tumour with very much lower uptake.

The specific activity of the autopsy specimens in this case are given in Table 3. The findings are similar to those with TRA 72 (MARRIEN, MARSHALL and MITCHELL 1961; MITCHELL 1961). The ratio of the specific activity of a specimen of tumour to that of red bone marrow is 4.0. Again it was noted that the macroscopic appearances of the tumour were very variable in different parts with great differences in the vascularity. The specific activity of the specimen of kidney was about the same as that of tumour. The values for the small intestine and testis were about half those for tumour and kidney, and about twice that for bone marrow. The value for liver was not high, being somewhat less than that for the small intestine. It is of interest that the values for specimens of brain are about the same as that for bone marrow. The detailed interpretation of these results is difficult. The tissues remaining for examination at autopsy are likely *a priori* to include a selection of cells which both are relatively radio-

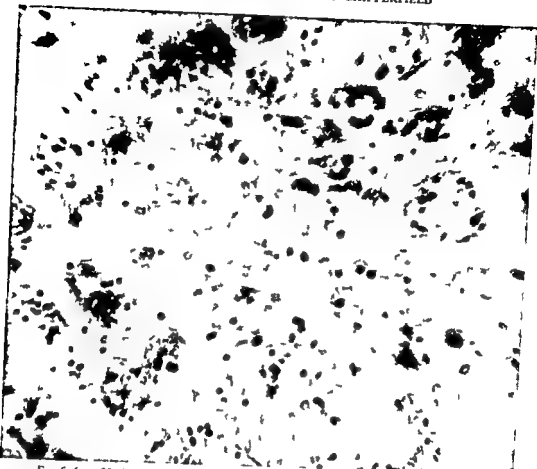


Fig. 6 Case 87. Autoradiograph of section of metastasis of carcinoma mammae. 1000

resistant and have shown a relatively low uptake of drug. The specimen of tumour showed severe degenerative changes almost certainly due to irradiation. For Case 86 of recurrent adenocarcinoma of the rectum the value of the microscopic D.A.R. for the biopsy specimen of tumour taken at 30 min after intra-arterial injection of 9.7 curies of TRA 119 was only 1.58. Histology showed rather widely separated tumour cells with some narrow spaces and very little stroma. The autoradiographs (Fig. 7) show labelling of apparently all the tumour cells but with wide variation from dense labelling of many to only slight labelling of others especially in some areas where probably the blood supply was poor.

Evidence concerning the distribution of the TRA 119 within the cells can be deduced from the autoradiographs. The limiting factor is the resolution, with which is associated the image spread. It is to be noted that the sections

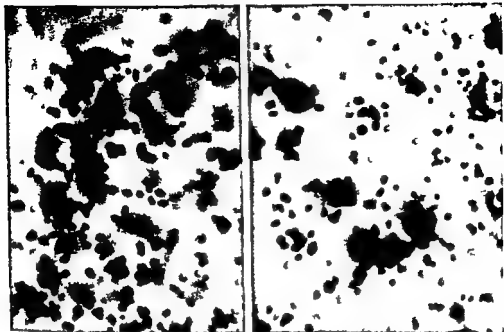


Fig 7 Case 86 Autoradiographs of section of metastasis of adenocarcinoma of rectum  $\times 1900$

of the cells are of thickness about  $5 \mu$  so that in relation to the range of the beta particles of tritium, the sections approximate closely to layers of infinite thickness. At a distance of  $5 \mu$  of unit density tissue from a point source of tritium the dose rate has fallen by a factor of about  $5 \times 10^{-4}$  (ROBERTSON and HUGHES 1959). The tumour cells show great variation in size. Representative mean values of the diameters are  $4.2 \mu$  for the nucleus and  $6.5 \mu$  for the cell (cf Case 66) and  $8 \mu$  for the nucleus and  $11 \mu$  for cell (cf Case 49). Under the experimental conditions the apparent grain size ranges from about  $0.4 \mu$  to about  $1.0 \mu$ . Tracks and parts of tracks are viewed at angles ranging over  $2\pi$ .

It is concluded that in most tumour cells the compound TRA 119 is present in the cytoplasm probably with concentration immediately outside and perhaps within the substance of the nuclear membrane, in some of these cells there is concentration in the regions of the nucleoli sometimes to a high degree. Apart from the nucleoli there appears to be little or no compound in most of the nuclei. Probably there is a high concentration in some cells in metaphase and anaphase chromosomes but this subject needs further investigation. There is almost certainly a higher concentration of compound in proliferating tumour cells than in the cells in non proliferating parts of the tumour. In most cases there appears to be negligible uptake in degenerating tumour cells. These findings are consistent with earlier studies of the distribution of Synkav it using flu

orescence microscopy (MITCHELL 1955) and also with the inhibition of part of RNA synthesis by SINKOVITZ (MARRIAN 1959)

The next part of the problem is the evaluation of the effective cell dose. The simplest model is to assume that the distribution of the compound, TRA 119, is uniform within the cytoplasm and nuclear membrane and that the cell and the nucleus are spherical. For a cell of diameter  $11\ \mu$  with nucleus of diameter  $8\ \mu$ , the D A R for the cytoplasm is increased in relation to that calculated for uniform distribution throughout the whole volume of the cell by a factor of 1.63, for a cell of diameter  $6.5\ \mu$  with nucleus of diameter  $4.2\ \mu$ , the D A R for the cytoplasm is increased by 1.37. These are not large factors. Moreover, it is likely that only the compound present in and immediately outside the nuclear membrane, meaning within a shell outside the nuclear membrane of thickness about  $1/2\ \mu$ , make an appreciable contribution to the dose delivered by the tritium to the nucleus and its contents. It is to be noted that at  $0.5\ \mu$  from a point source of tritium, the dose rate has fallen to about 8% (ROBERTSON and HUGHES 1959). It is difficult to estimate the effects of irradiation by tritium in the regions of the nucleoli. However the high degree of radiosensitivity of the nucleoli, as shown in microbeam studies (SEED 1960), must be noted. Even if it is assumed that half the tritium in the cell is concentrated in a spherical shell of thickness  $0.5\ \mu$  surrounding the nuclear membrane the dose of radiation delivered within the nucleus near the inner surface of the nuclear membrane is such that it is not likely that the effective value of the D A R is raised above the average cell value by a factor of more than about 1.5, or less for small cells. It seems reasonably certain that a substantial proportion of the nuclear contents receive only a small or negligible dose of radiation.

These considerations suggest that until much more precise information is available, the best approximation to make is to assume that the relevant values of the specific activity and the D A R correspond to the macroscopic values averaged over tumour cells. This procedure may in some cases underestimate the mean value of the dose averaged over all tumour cells. This use of the mean value is open to the objection that viable tumour cells with uptake much less than the average value may receive inadequate doses of radiation. To some extent, this factor can be assessed by autoradiography in terms of the distribution of grain counts per cell. It may be offset to a certain extent by the persistence of tritium in the tumour cells irradiated at lower dose rate. Nevertheless, this problem of low dosage in some of the tumour cells is important and may prove to be the factor limiting the possibility of cure by means of a radioactive drug.

Within the limitations discussed, it is now possible to consider the approximate estimate of the mean dose of radiation received by the tumour cells in the selected cases.

For Case 66, of recurrent adenocarcinoma of the caecum the relevant mean specific activity of the tumour cells had the value of about  $600\ \mu\text{C per gram}$

This corresponds to an initial dose rate of about 176 rad per 24 hrs which is equivalent biologically, assuming the value of 1.7 for the P.B.L., to about 300 r of  $^{60}\text{Co}$  gamma radiation per 24 hours. However, the B.H.L. of the tritium in the tumour in this case was only about 1.4 days so that it was only possible to deliver a total dose of about 600 r corresponding to the mean life of about 2 days. This conclusion is in agreement with the clinical observation that no improvement followed the intravenous injection of 9.9 curies of TRA 119. The possibility of repeated intravenous injections must be raised in retrospect although it is unlikely that a therapeutically useful dose of radiation could have been delivered in this case.

For Case 49 of recurrent adenocarcinoma of the rectum, it has been shown that the D.A.R. for the tumour cells had a value of not less than 8. Accordingly, the relevant specific activity of the tumour cells is about 226  $\mu\text{C}$  following the intravenous injection of 1.4 curies of TRA 119 using a preparation containing about 8 mg of compound. The initial effective dose rate is thus at least about 112 r per 24 hours. With a long B.H.L. not inconsistent with a value of 13 days or even longer as suggested by the findings in autopsy specimens, it is not unreasonable to expect some palliative effect of the radiation delivered. Moreover, it is likely that by intravenous injection of 8 curies of TRA 119 corresponding to the amount of 11 curies per 70 kg of body weight which is now considered justifiable, an initial dose rate corresponding to about 640 r per 24 hours would have been attained in the tumour cells.

For Case 80 of recurrent carcinoma mammae, the value of the specific activity of the tumour cells must be taken as 103  $\mu\text{C}$  per gram, although it is realised that this may be an underestimation. The equivalent initial dose rate is thus at least 53 r per 24 hours. Even assuming a long B.H.L. for the tritium in the tumour cells, it seems doubtful whether the observed relief of pain could be attributed to irradiation at this dose level. The amount of 10.1 curies of TRA 119 injected intravenously was contained in 74 mg of the chemical compound ordinary Synkavit even in larger amounts does not relieve pain in these cases. The question of a psychologic effect must be raised but the possibilities of radiosensitization and of underestimation of the cell dose must be considered.

The selected cases treated by intra-arterial injection raise many problems. For Case 52 of recurrent nodules of malignant melanoma, it must be emphasised that there is no evidence of the delivery of equivalent dose rates of radiation of more than about 40 r per 24 hours from each of the three intra-arterial injections. However, in view of the observed late retrogression of the secondary nodules, the possibility of a very long B.H.L. of the tritium in the tumour cells must be considered but the question of spontaneous retrogression must be raised.

For Case 71 of extensive recurrent squamous carcinoma of the pinna of the ear, the high values of the specific activity in the tumour cells are consistent with the delivery of doses of radiation at the therapeutic level. The remarkably



high value of  $8\,990\ \mu\text{C}$  per gram found for the 30 min biopsy from the anterior part of the lesion is probably only a short lived concentration. With the poor circulation through the tumour observed in this case, the values of the specific activity for the biopsy specimens at  $3\frac{1}{2}$  hrs after the intra-arterial injection of 10.8 curies of TRA 119 are likely to give more reliable estimates of the doses of radiation delivered. For the biopsy from the anterior part of the lesion, the specific activity of  $378\ \mu\text{C}$  per gram corresponds to an effective dose rate of 188 r per 24 hrs, for the biopsy from the posterior part of the lesion, the specific activity of  $1\,815\ \mu\text{C}$  per gram corresponds to a dose rate of 904 r per 24 hrs. The specific activity of the autopsy specimen is not inconsistent with a value of the B.H.L. of about  $1\frac{1}{2}$  days. Accordingly, on the basis of a value of about 6.3 days for the mean life of the tritium in the tumour, the total doses delivered would be about 1 200 r for the anterior part of the lesion and about 5 700 r for the posterior part. It is to be noted that the anterior part of the lesion with the very poor blood supply was in the area previously treated by external radiotherapy. The results for the biopsy specimen from the unirradiated posterior part of the lesion suggest that it may be possible to deliver a curative dose of radiation to a squamous carcinoma by means of intra-arterial TRA 119.

The results for Case 86, of recurrent adenocarcinoma of the rectum, are disappointing, perhaps because of the poor blood supply to the recurrent mass in the ischio-rectal fossa and perineum, but possibly because the tumour bed area was washed through with 50 ml of saline immediately before the intra-arterial injection of, first Priscol, and then the TRA 119. The equivalent dose rate delivered was about 114 r per 24 hours, which could be expected to produce some palliative effects if associated with a long B.H.L. of the tritium in the tumour cells. Temporary relief of pain was in fact observed.

### General discussion and Conclusions

The results provide evidence for some degree of selective concentration of TRA 119 in the tumour cells in relation to normal cells in some cases of certain types of malignant disease. The estimated doses of radiation delivered by the tritium are consistent with the clinical finding that after intravenous injection of TRA 119, palliative effects may be produced in cases of highly radiosensitive conditions such as testicular seminoma and Hodgkin's disease, and also in certain cases of slowly progressive recurrent adenocarcinoma of the gastro-intestinal tract.

Intra-arterial administration of TRA 119 appears to be necessary to attain therapeutic levels of the dose of radiation in the attempted treatment of patients with relatively localised but otherwise untreatable malignant disease of the histologic types of squamous carcinoma, melanoma and adenocarcinoma. The

present evidence together with that of earlier studies with TRA 72, suggests the desirability of further investigation of the possible value of intra arterial therapy with TRA 119 in selected otherwise untreatable cases of squamous carcinoma of the head and neck, and also of the parametrium in carcinoma of the uterine cervix, stage III, malignant tumours of the limbs including melanoma and tumours of bone, and adenocarcinoma of the gastrointestinal tract

It is clear that much further investigation of the dose and time factors is required, particularly in connection with the need for repetition of intra arterial injections at intervals comparable with the biologic mean life of the tritium in the tumour. In order to slow down the rate of blood flow through the tumour the suggestion has been made by our colleague Dr Aileen K. Adams, that the intra arterial injection should be given under hypothermia.

From a biochemical point of view, the selective uptake of TRA 119 into certain malignant cells is of interest particularly in relation to the recent findings of low concentrations of co enzyme Q in some tumours, and of the greater increase in the activity of certain oxidative enzymes produced by addition of co enzyme Q<sub>10</sub> or menadione in tumour than in homologous normal tissue (WATTENBERG 1961 OSTERBERG and WATTENBERG 1961)

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### SUMMARY

An account is given of laboratory and clinical investigations of the therapeutic possibilities of a radioactive drug containing tritium in very high specific activity, 2-methyl-5,6,7-tritio-1,4-naphthoquinol bis (disodium phosphate) (TRA 119). Measurements of the specific activity of biopsy and autopsy specimens and autoradiographic studies are discussed in selected cases with special reference to dosimetry. The results provide evidence for some degree of selective concentration of TRA 119 in tumour cells in relation to normal cells in some cases of certain types of malignant disease.

## ZUSAMMENFASSUNG

Laboratoriums und klinische Untersuchungen über die therapeutische Wirksamkeit eines radioaktiven Heilmittels das stark aktive Tritium 2 Methyl 5 6 7 Tritio-1 4 N phthaquinol bis (disodiumphosphat) (TRA 119) enthält werden beschrieben. Messungen der spezifischen Aktivität nach Probeexzision auf dem Sektionstuch und autoradiographische Untersuchungen in ausgewählten Fällen werden geschildert mit besonderer Rücksicht auf die Dosimetrie. Die Resultate bestatigen die selektive Konzentration des TRA 119 in den Tumorzellen von gewissen Arten von malignen Geschwülsten.

## RÉSUMÉ

Présentation des études expérimentales et cliniques sur les possibilités thérapeutiques d'une substance radioactive contenant du tritium de très haute activité spécifique le 2 méthyl 5 6 7 tritio-1 4 naphthaquinol bis (phosphate disodique) (TRA 119). Les auteurs examinent, en particulier au point de vue de la dosimétrie sur des cas sélectionnés les mesures de l'activité spécifique de pièces biopsiques et autopsiques et les études autoradiographiques. Les résultats donnent la preuve d'une certaine concentration sélective du TRA 119 dans les cellules tumorales par rapport aux cellules normales dans certains cas de certains types d'affection maligne.

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## GONAD DOSIMETRY IN DIAGNOSTIC RADIOLOGY WITH THE HIGH KILOVOLTAGE TECHNIQUE

by

HERMANN BOSCHKE and SVEN ROLAND KJELLBERG

Radiography at kilovoltages of 150 or higher may in many circumstances possess certain advantages. Reductions in the exposure time and the subsequent radiation dose are obtained and by the use of a small tube focus better image definition may be obtained.

The main objection to the so called high kilovoltage technique would appear to be the cost involved in changing from a conventional radiographic technique but the only valid argument against the high kilovoltage technique advanced by various investigators would appear to be that the gonad dose increases 3 to 5 times when the kilovoltage rises.

As previous results obtained in our department did not confirm this assertion the results of a new and extensive investigation are now presented.

The following preliminaries to the tests took place:

1. Checking of the roentgen equipment and of the exposure factors ( $kV \cdot mA \cdot sec$ ). Negligible  $mA$  deviations will be considered in this report. Cable capacity = 770 picofarads per meter.
2. Checking of instruments: (a) Philips electrometer type 37471/00 with measuring chamber 0.30-300 r/min type 37480/10 HVL 0.03-4 mm Cu for the test measurements and with chamber 1.3-10 r/min type 37488/10 HVL 0.07-2 mm Cu for SD/ED/FD measurements; (b) EIL electrometer (Electronic Instruments Ltd) model 378 with standardized round graphite flat chamber  $5 \times 13$  cm. Chamber constant at 22 and 760 mm Hg = 1.00 for  $mR$  values. The variation of the chamber for the various voltages was less than 3%.

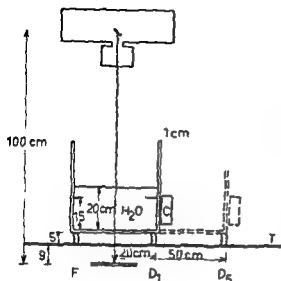


Fig. 1. Experimental model.

3. Checkup of the densitometer EEL Universal for constant sensitivity extended over a few days.

The abbreviations used are as follows:

SD = superficial dose

FD = film dose (in film plane)

sF = small field 10 × 10 cm collimated at the phantom base

LF = large field 15 × 15 cm collimated at the phantom base

CCD = chamber-central beam-distance

S = film blackening

FD = exit dose

GD = gonad dose

Testing arrangements (see Fig. 1):

1. Siemens diagnostic tube 200 kV, 30.0 kW large focus of 1 mm with a filter of 0.2 mm Fe. 5664 exposures had been made with this tube at the beginning of the investigation.

2. Elema Schonander Triplex Optimate three phase generator 150 cycles with additional transformer. Minimum switching time 1.53 msec (with due consideration to cable capacity).

3. Elema Schonander Coordinat Universal table with Elema grid 7.1.

4. Gevaert Rapid film and Schmidthal's cassettes with Siemens Rubin intensifying screens.

5. Elema Jarnh automatic film processing machine type 7.

6. Phantoms of 1 cm plexiglass 40 × 40 cm and 30 × 30 cm with 15 cm or 0 cm water depth.

7. Distances: Focus-film 100 cm, focus-table 91 cm, focus-phantom 86 cm, focus-water surface 71 or 66 cm.

8. Field collimation at the phantom base with Siemens collimator.

9. Measuring points: the middle of the chamber in the central beam on the water surface = SD, the middle of the chamber in the central beam on the bottom of the phantom = ED, the middle of the chamber in the central beam on the film plane = FD, chamber on the lateral wall at half water height at a distance of 20 to 50 cm from the central beam = GD.

### Test series

The test series were tabulated in proper sequence. In the evaluation only the results of complete test series that had given constant values in repeated measurements after elimination of initial sources of error were used. Preliminary tests provided identical relationships between values.

All measurements were made under the same initial conditions. In order to ensure constant radiographic data, constant film blackening was required for the voltage steps from 60 to 190 kV.

### Measurements

1. Determination of radiographic data by adjusting the mA value and time factor (sec) to 60, 80, 110, 140, 190 kV. One series with a film blackening of 0.6 and another one of 1.3 was obtained.

2. Measurement of the superficial dose, exit dose and film dose related to a film blackening of 0.6 and 1.3 with a small and a large field and in a 15 cm water phantom.

Table 1

Comparison of the film blackening with various intensifying screens

kV	mA	sec	Blackening of the film		
			Screen 1*	Screen 2	Screens <sup>3</sup>
60	200	1.0	0.77	0.65	1.10
80	200	0.2	0.80	0.65	1.10
120	200	0.02	0.74	0.60	0.9,
150	200	0.007	0.72	0.55	0.5,
200	200	0.003	0.75	0.60	1.10

\* This screen was used in the experiments

<sup>3</sup> Checking and correction of exposure data because of excessive variation

<sup>4</sup> Measurement of film dose related to a film blackening of 0.6 and 1 large field and in 15 cm water with corrected values

<sup>5</sup> As under (4) but in 20 cm water

<sup>6</sup> Determination of new exposure data related to a film blackening of 0.7 mA was kept constantly at 200 and the exposure time (sec) was adjusted. These data were used for the following tests Nos 7 to 14

<sup>7</sup> Measurement of superficial dose exit dose film dose with 0.2 mm filter a small and large field and 15 cm water (Tables 2 and 3)

<sup>8</sup> Measurement as under (7) but with 20 cm water (Tables 5 and 6)

Table 2

Relation SD ED FD in 15 cm water and field  $10 \times 10$  cm with 0.2 mm filter

Filter	Surface dose in mr		Exit dose in mr	
	Fe	Without	Fe	Without
60 kV	79.0	173.0	1.30	2.20
80 kV	34.0	68.0	0.70	1.12
110 kV	31.5	38.2	0.64	0.91
140 kV	23.5	30.9	0.60	0.71
190 kV	21.2	31.5	0.64	0.79

Table 3

Relation SD ED FD in 15 cm water and field  $15 \times 15$  cm with 0.2 mm filter

Filter	Surface dose in mr		Exit dose in mr	
	Fe	Without	Fe	Without
60 kV	103.0	205.0	1.39	2.20
80 kV	44.2	70.1	0.72	1.12
110 kV	27.0	44.1	0.34	1.7
140 kV	23.4	33.0	0.32	1.20
190 kV	22.5	32.7	0.36	1.20



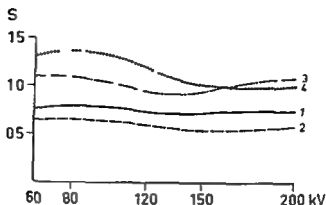


Fig. 2. Relation of film blackening with different screens and same exposure data (screen 1 was used for the experiments).

9. Measurement of gonad dose with 0.2 mm Fe filtration and without filter: small and large field, 15 cm water with 20, 30 and 50 cm chamber central beam distance.

10. Measurement of gonadal dose as under (9) but with 20 cm water.

11. Control measurement of film blackening and exposure factors. For comparison, 4 different screens were used. Screen combination 1 gave the most constant film blackening and was therefore used in the examinations (Table 1, Fig. 2).

12. Exposure data unchanged: repeat measurements of gonadal dose as under (9). Chamber central beam distance 20, 25, 30, 35 and 50 cm (Tables 6 and 7, Figs 3 and 4).

13. Repetition of the measurements as under (10): distance as under (12) (Tables 8 and 9, Figs 5 and 6).

14. Control measurement of superficial dose: curve in the range between 40 and 60 kV with and without filter.

Exposure data were determined with an average film blackening of 0.74 for tube potentials of from 60 to 80 kV (Table 1).

A comparison of the blackening characteristics obtained with various intensifying screens confirm the radiographic data and the constant behaviour of the selected screen combination 1 with reference to film density (Table 4, Fig. 2).

The values shown in Tables 2 and 3 indicate a steep drop in the superficial dose, especially between 60 and 120 kV. The curve of the filtered radiation runs nearly parallel to that representing the unfiltered radiation.

The values in Tables 4 and 5 have a relationship similar to those in Tables 2 and 3. In the case of 15 cm water and a small field, the exit dose is reduced to a fifth in the voltage range from 60 to 140 kV and in the case of 20 cm water and a large field the exit dose decreases to a fourth within the same voltage range. A slight increase in the exit dose is observed in the voltage range from 140 to 190 kV in both tests and this increase corresponds to a small measurable lower vol

Table 4

Relation SD FD in 20 cm water and field  $10 \times 10$  cm with 0.2 mm iron filter and without filter

Filter	Surface dose in mr		Exit dose in mr		Film dose in mr	
	Fe	Without	Fe	Without	Fe	Without
60 kV	100.0	225.0	3.04	4.21	0.19	0.26
80 kV	42.0	74.4	2.13	2.90	0.13	0.20
110 kV	38.0	47.0	1.13	1.21	0.09	0.12
140 kV	29.0	39.0	1.05	1.07	0.18	0.16
190 kV	23.5	38.7	1.12	1.20	0.15	0.20

Table 5

Relation SD ED FD in 20 cm water and field  $15 \times 15$  cm with 0.2 mm iron filter and without filter

Filter	Surface dose in mr		Exit dose in mr		Film dose in mr	
	Fe	Without	Fe	Without	Fe	Without
60 kV	112.0	245.0	4.90	6.81	0.30	0.42
80 kV	48.0	83.0	3.12	4.21	0.22	0.31
110 kV	43.0	48.0	1.83	2.02	0.17	0.20
140 kV	31.2	40.2	1.51	2.00	0.20	0.25
190 kV	29.0	38.0	1.65	1.80	0.22	0.30

ume dose. The 'sag' of the curve for the film dose in the range from 60 to 120 kV is based on the decrease of the absorption factor of the grid/cassette combination and on the increased luminescence of the intensifying screens. The increase within the voltage range up to 190 kV is obviously related to the harder radiation.

With reference to a constant film density and the radiographic data in accordance with Table 1, it is evident from Fig. 3 and Table 5 that the gonad dose decreases with the distance from the central ray in the various kV ranges, the lower the voltage the more marked will this decrease be. The shape of the curves corresponding to a specific distance from the central ray reveals that with rising voltage the gonad dose drops considerably. Its minimum value is obtained at voltages of from 110 to 140 kV; the increase with voltages of up to 190 is only slight and does not exceed the dose level obtained at 100 kV.

The measurement values in Fig. 4 and Table 7 show that the larger field influences the absolute values but not their interrelation. Here again the gonad dose is markedly higher at 60 and 80 kV than at voltages higher than 100 kV. The bundle of curves is denser with a 20 cm water phantom corresponding to a thick patient although the shape of the curves compared with findings of the previous test is not altered. Here again the minimum value of each curve falls in the voltage range from 110 to 140 kV and the slight rise with voltages

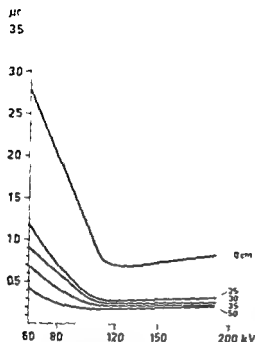


Fig 3 Gonad doses with 60 to 190 kV at different distances from field 15 cm water field 10 x 10 cm (see table 6)

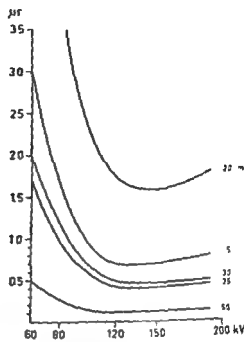


Fig 4 Gonad doses with 60 to 190 kV at different distances from field 15 cm water field 15 x 15 cm (see table 7)

up to 190 lies far below the values measured at voltages lower than 100 kV (Fig 5, Table 8). The gonad dose at 60 kV is 3 to 6 times greater according to the distance from the central ray than the one measured at 190 kV. The increased scatter of the larger field results in a somewhat more marked rise in the gonad dose at 190 kV (Fig 6, Table 9), but it completely corresponds to the equally higher value obtained at 100 kV. The gonad dose at 60 kV is still about 3 times higher at all distances measured than at 190 kV.

### Results

The values given in Tables 2, 3, 4 and 5 indicate the behaviour of the superficial dose, exit dose and film dose at voltages from 60 to 190 kV in relation to a constant film dose blackening.

The steep drop in the superficial dose with increasing radiographic voltage has been confirmed by all research workers. Because of the backscatter, which has also to be measured, the dose on the phantom's surface is higher than when the measuring chamber is located in the same position but without a phantom. This was previously shown by SCHAAAL.

Table 6

*Gonad doses in  $\mu\text{r}$  in 15 cm water and field size  $10 \times 10$  cm with 0.2 mm iron filter at different distances from field*

kV	Chamber — central beam — distances				
	50 cm	35 cm	30 cm	25 cm	20 cm
60	4.4	7.0	9.1	12.0	28.0
80	2.4	4.5	6.3	7.2	20.0
110	1.8	2.2	2.4	2.8	8.2
140	2.0	2.1	2.3	2.7	7.2
190	2.2	2.3	2.5	3.2	8.3

Table 7

*Gonad doses in 15 cm water and field size  $15 \times 15$  cm with 0.2 mm iron filter at different distances from the field*

kV	Chamber — Central beam — Distances				
	50 cm	35 cm	30 cm	25 cm	20 cm
60	5.0	17.5	20.0	30.0	60.0
80	2.8	10.0	12.0	17.0	38.0
110	1.3	4.7	5.4	7.7	20.0
140	1.3	4.2	4.9	7.2	16.0
190	1.3	4.5	5.0	8.0	18.0

Doses in  $\mu\text{r}$

The exit dose follows by no means a linear course in relation to the constant film density required in practice. The exit dose drops at 190 kV on an average by a third of the value obtained at 60 kV when various field sizes and object thicknesses are used. The total volume dose is lessened owing to the more favourable relationship between superficial dose and exit dose in the case of rising voltages. The film dose from its initial value obtained at 60 kV decreases up to 110 kV and rises again slightly with voltages up to 190 kV. The fact that the curve does not follow a rectilinear course proves that the film density is a function of the kilovoltage. There is a decrease in the film dose of 30 to 40 % when the potential is raised from 60 to 190 kV, depending on the object thickness and field size.

The gonad dose curves (Figs 3, 4, 5 and 6) obtained by plotting the measured values (Tables 3, 4, 5, 6, 7, 8 and 9) display a uniform course despite irregularities caused by measuring errors. A high scatter dose is measured at 60 kV at distances of 20, 25, 30, 35 and 50 cm from the central ray. This dose has reached its half value at about 80 kV. The lowest point of all curves for the various phantom thicknesses and field sizes is obtained between 140 and 110 kV; this lowest value moves from 140 kV at a distance of 20 cm to

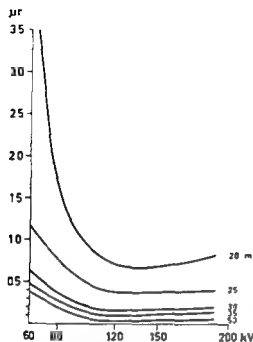


Fig 5 Gonad doses with 60 to 190 kV at different distances from field 20 cm water field  $10 \times 10$  cm (see table 8)

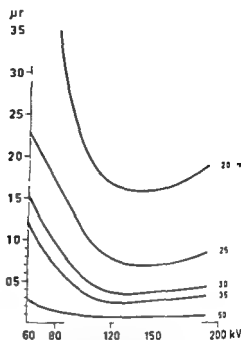


Fig 6 Gonad doses with 60 to 190 kV at different distances from field 20 cm water field  $15 \times 15$  cm (see table 9)

110 kV at 50 cm. When the radiographic voltages are pushed up to 190 kV, the curves become slightly steeper, because under this condition the effect of the increased harder scatter is felt. This rise is however so small that the end of the curve at 190 kV does not exceed the value obtained at 100 kV. The flat end of the curve represents only a moderate change in the gonad dose between 110 and 190 kV as compared with the steep rise at the beginning of the curve. Moreover, the curves give the impression that it is the field size rather than the phantom thickness that affects the gonad dose.

### Discussion

These measurements of the superficial dose and exit dose correspond with the data obtained by other authors. The values differ only in their absolute magnitude. The present writers used for all kV ranges tested added filtration of 0.2 mm Fe. With regard to the resultant radiation homogeneity, this corresponds to 4 mm Al filtration but offers in compensation a gain in dose rate (1, 2).

Grids, filters, intensifying screens and films remained constant during the tests. There is no doubt that a higher blackening and a modification of the grid filter, intensifying screen or film, change the measured values in their order of magnitude although the type of curves obtained will be maintained.

Table 8

*Gonad doses in 20 cm water and field size  $10 \times 10$  cm with 0.2 mm iron filter at different distances from the field*

kV	Chamber — Central beam — Distances				
	50 cm	30 cm	30 cm	25 cm	20 cm
60	3.8	4.9	6.5	12.0	43.0
80	2.1	2.8	3.8	7.8	17.0
110	0.35	1.4	1.9	4.2	8.0
140	0.4	1.3	1.9	3.8	7.0
190	0.5	1.4	2.0	4.1	8.0

Doses in  $\mu$ r

Table 9

*Gonad doses in 20 cm water and field size  $15 \times 15$  cm with 0.2 mm iron filter at different distances from the field*

kV	Chamber — central beam — distances				
	50 cm	30 cm	30 cm	20 cm	20 cm
60	2.7	12.0	15.0	23.0	51.0
80	1.5	7.0	9.8	17.0	30.0
110	0.75	2.8	4.3	9.0	18.0
140	0.8	2.8	3.8	7.0	16.0
190	0.9	3.2	4.6	8.5	19.0

Doses in  $\mu$ r

The impression gained by the writers that the thickness of the patient has only a slight influence on the gonadal dose values in conjunction with HAY-BITTLE's statement that the field size is not as decisive as the distance of the gonads from the field suggests that the characteristic shape of the curves obtained make them generally acceptable for roentgen diagnosis.

Many papers dealing with the changes in the gonad dose with varying radiographic potential have appeared. The results are by no means uniform and the reports that the gonad dose increases by as much as 3 to 5 times when the tube potential is raised into the high kV range is limited to few yet frequently quoted test results. These papers almost without exception referred to a constant exit dose obtained in phantom measurements. In contrast to this it emerges from Tables 2, 3, 4 and 5 that the exit dose is not suitable as a reference point if the present conditions are to be met. OESER found in phantom measurements at tube potentials up to 100 kV that the gonad dose appreciably rises in the high kV ranges. With reference to the exit dose MOHR arrived at the same results by phantom measurements at kilovoltages up to 200 kV. Accounts by the same author on results obtained in patients during examinations made by

operators in various hospitals under different conditions are not conclusive as he indicated only mean values for potentials up to 150 kV. MICHAEL & SVOBODA, while emphasizing the advantages of high kV technique for phantom measurements with a constant exit dose, also drew the conclusion that the gonad dose increases. SCHAAAL however found that the increase in the gonad dose is less marked if the measurements are made behind the grid a result which was confirmed by measurements effected by MOHR. CEN & FRIK in making measurements under the same conditions also observed that the gonad dose rises with a higher tube potential but argued that this increase might possibly be affected by the grid intensifying screen and film factors. KLOTZ & SEELENTAG, in a thesis published in 1961, stated that during measurements made in a living subject the gonad dose increased with rising potential, but laid the emphasis of the investigation on the resultant dosages actually obtained in routine examinations. KLOTZ (1958) however, reported that the difference in the magnitude of the gonad dose with soft and hard radiation (50 to 200 kV) is not noticeable although he too referred to a constant exit dose. There appears to be a contradiction in the paper of MARTIN who in a table for thorax radiography gave a reduction of the dose to the ovaries when the radiographic voltage and the filtration were raised. Mention is made in the pertinent text however of an increase in the gonad dose under the same conditions. Detailed voltage and filtration data are not available in the clinical application of these investigations.

It emerges from a large number of publications (BURNET, HAMMER, JACOBSEN, HOLTHUSEN, OSBORN, WINDEYER, ZUPPINGER et coll.) that the gonad dose received in roentgen diagnosis is on an average very small, it is also lower than the dose received from the daily exposure to natural ambient radiation. Consequently a dose increase or decrease certainly lies within a magnitude that in itself can be tolerated. It must be stressed however, that this knowledge does not free us from the obligation of keeping the individual dose of the patient as low as possible.

Although the results contained in the publications that have been quoted only in part are not uniform, they have nevertheless produced the impression that the higher gonad dose should restrict the use of high kilovoltages. The present results corroborate the fact, already presumed in some papers, that the gonad dose does not rise when radiographic voltages in the high kV range are employed. More than that, they demonstrate that at the distances used in daily practice, the gonad exposure is considerably higher at voltages from 60 to 100 kV than from 100 to 200 kV.

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## SUMMARY

The superficial exit and scatter doses corresponding to the gonad dose were measured in a phantom at kilovoltages of from 60 to 190 kV with a tested installation and under given conditions. Proof was obtained that the gonad dose decreases both at short and long distances when the tube potential is increased. The gonad dose is considerably higher at radiographic voltages from 60 to 80 kV than in the 100 to 200 kV range.

## ZUSAMMENFASSUNG

An einem Phantom wurden die Einfallsstrahlung, die Ausfallstrahlung sowie die Streuung bei Verabreichung einer Gonadendose bei Spannungen von 60 bis 190 kV mit einer geeichten Apparatur und unter kontrollierten Bedingungen gemessen. Es wurde bestätigt, dass die Gonadendose sowohl bei kurzen als auch bei langen Abständen abnimmt, wenn man die Röhrenspannung vergrößert. Die Gonadendose ist beträchtlich höher im Bereich der diagnostischen Spannungen von 60 bis 80 kV als im Bereich der Hartstrahltechnik von 100 bis 200 kV.

## RÉSUMÉ

La dose superficielle, la dose de sortie et la dose de rayonnement diffusé correspondant à la dose gonade ont été mesurées sur un fantôme sous des tensions comprises entre 60 et 190 kV avec une installation testée et dans des conditions déterminées. Cette expérimentation prouve que la dose gonade diminue aussi bien à courte qu'à longue distance quand la tension du tube augmente. La dose gonade est considérablement plus élevée à des voltages radiographiques compris entre 60 et 80 kV qu'entre 100 et 200 kV.

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## MINERAL PATTERN OF URINARY CALCULI FROM GERM FREE RATS

by

J. E. GLAS and B. GUSTAFSSON

A frequent occurrence of urinary calculi was detected in a recent investigation in germ free rats (GUSTAFSSON & NORMAN 1962). Profound alterations in the urinary composition were found to be associated with the presence of numerous bladder stones which were observed almost exclusively in males. When the animals acquired the flora of conventional rats however the urinary excretion after a short period returned to normal. Conventional rats maintained on exactly the same diet were entirely free of calculi indicating that some specific etiologic factor for stone deposition was present under germ free conditions. The present report concerns the morphology, structure and mineral composition of bladder stones collected from a small number of germ free rats.

*Germ free method.* Germ free rats were reared according to the modified technique of GUSTAFSSON (1948, 1959) and maintained on the semisynthetic diet D7 sterilized by autoclaving for 20 min at 121°C. According to the analysis of the diet by a commercial laboratory the dry weight basis consisted of protein 21.4%, calcium 1.02%, phosphorus 0.48% giving a Ca/P ratio

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## MINERAL PATTERN OF URINARY CALCULI FROM GERM-FREE RATS

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J E GLAS and B GUSTAFSSON

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*Germ free method* Germ free rats were reared according to the modified technique of GUSTAFSSON (1948, 1959) and maintained on the semisynthetic diet D7 sterilized by autoclaving for 20 min at 121 °C. According to the analysis of the diet by a commercial laboratory the dry weight basis consisted of protein 21.4 %, calcium 1.02 %, phosphorus 0.48 %, giving a Ca : P ratio

of 2.13 The animals were killed after various periods of time and the bladder stones were collected and kept at  $-17^{\circ}\text{C}$

*Roentgen analysis* One to five calculi from each animal were examined by the powder roentgen diffraction technique. The stones were cut in two equal halves, one of which was ground into a fine powder. Representative samples, containing all the components present in each calculus were thus assumed to be obtained. Diffraction patterns from such specimens were recorded with a cylindric Debye Scherrer camera 114.6 mm in diameter. Ni filtered Cu radiation from a roentgen tube, operated at 40 kV and 20 mA was used throughout the diffraction experiments. The cut surface of the remaining halves of the stones was ground as smooth as possible and a slice was cut parallel to the ground surface. The ground sections obtained in this way had a thickness between 200 and 300 microns and were obtained from calculi from the majority of the rats. In most cases regions having a different microscopic appearance were noted in the cut sections and small pieces of such regions were dissected out for identification, a flat film microroentgen diffraction camera being used for this purpose. Contact microradiograms of the sections were made prior to the dissection procedure on Kodak Maximum Resolution plates using Ni filtered Cu radiation as above. These provided detailed information, due to the varying roentgen absorption characteristics, on the local distribution of the different chemical components building up the calculi.

The crystalline salts present within the calculi were identified after comparing diffraction patterns from substances of known composition with those actually obtained from the stones. Identification of one of the components (calcium citrate hexahydrate) was somewhat complicated by the lack of reference material as well as of recorded roentgen data for the particular hydrate present. Several different preparations of different hydrated forms of calcium citrate were therefore produced, diffraction patterns from such precipitates (dried at room temperature for 48 hours) were recorded and compared with those obtained from the calculi.

### Results and Discussion

Bladder stones from germ free animals appeared as well formed ovoid to spherical bodies varying in size from less than 0.5 mm to 7 mm. The number and approximate size distribution of stones collected from five rats of different ages are given in the Table. The external appearances and internal structure of calculi from each animal were identical, as revealed by microscopic examination of intact or fractured/sliced stones in reflected light. Calculi collected from a single animal also showed uniform chemical characteristics.

Three different chemical compounds were identified in the calculus material examined: calcium citrate hexahydrate ( $\text{Ca}_3(\text{C}_6\text{H}_5\text{O}_7)_2 \cdot 6\text{H}_2\text{O}$ ), calcium

Table

*Numbers and size distribution of stones collected from five rats of different ages*

Animal No	Age at sacrifice (days)	Number and size of calculi	Number of calculi examined	Components found in the calculi
1	128	2 2 to 3 mm	1	Calcium oxalate dihydrate
2	104	8 to 10 0.5 to 4 mm	5	Calcium citrate hexahydrate + calcium oxalate dihydrate
3	208	8 to 10 0.5 to 3 mm	4	Calcium citrate hexahydrate + calcium oxalate dihydrate
4	974	20 to 25 2 to 7 mm	4	Calcium citrate hexahydrate + calcium oxalate dihydrate + basic calcium phosphate (apatite)
5	110	*0.5 to 4 mm	2	Calcium citrate hexahydrate + calcium oxalate dihydrate

\*Cluster of ovoid stones connected by masses of calculus material

oxalate dihydrate ( $\text{CaC}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$ ) and basic calcium phosphate, 'apatite' ( $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ ) (see Table). The presence of the hexahydrate modification of calcium citrate within the stones was strongly suggested by the observation that a change in crystal structure from that of the tetrahydrate form was induced after the calculus citrate had been heated to 60°C for two hours. The predicted temperature for the hexahydrate-tetrahydrate transformation is 52°C, as shown by CHATTERJEE & DHAR (1924). Moreover, diffraction patterns obtained from calcium citrate precipitates dried at room temperature and containing 6 l moles of water were found to be identical with those recorded from the calculus citrate, thus proving the existence of the hexahydrate modification in the stones. Citrate occurred as the dominating component in the calculi and appeared as a white, soft and rather loosely packed powder which easily decomposed into thin, curved lamellae when fractured. Calcium citrate was occasionally found in the pure state in small volumes although it usually occurred admixed with calcium oxalate and sometimes apatite.

Only in one case were stones found to be composed of pure calcium oxalate. Calculi from animal 1 thus appeared as a cluster of closely connected brownish crystals arranged radially and having an individual size of about 100 to 400 microns.

In calculi from other animals, calcium citrate always formed a central core in combination with varying quantities of calcium oxalate. The oxalate fraction mixed with the citrate, however, was always small and showed up in the microdiffraction patterns as spotty rings indicating a greater crystal size than the citrate.

As judged from microradiograms and microroentgen diffraction tests, there was an increasing proportion of oxalate towards the outer parts of the stones in most cases. Calculi from animals 2, 3 and 4 were all enveloped with a thin

of 2 13 The animals were killed after various periods of time and the bladder stones were collected and kept at  $-17^{\circ}\text{C}$

**Röntgen analysis** One to five calculi from each animal were examined the powder roentgen diffraction technique The stones were cut in two halves, one of which was ground into a fine powder Representative samples containing all the components present in each calculus, were thus assumed to be obtained Diffraction patterns from such specimens were recorded in a cylindric Debye Scherrer camera, 114.6 mm in diameter Ni filtered radiation from a roentgen tube, operated at 40 kV and 20 mA was used throughout the diffraction experiments The cut surface of the remaining halves of the stones was ground as smooth as possible and a slice parallel to the ground surface, the ground sections obtained in this way had a thickness between 200 and 300 microns and were obtained from the majority of the rats In most cases, regions having a different microscopic appearance were noted in the cut sections and small pieces of regions were dissected out for identification, a flat film microroentgen camera being used for this purpose Contact microradiogram sections were made prior to the dissection procedure on Kodak N Resolution plates, using Ni filtered Cu radiation as above These detailed information, due to the varying roentgen absorption characteristics on the local distribution of the different chemical components within the calculi

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analysis involving the use of column and gas chromatography for the separation and identification of calcium oxalate and calcium citrate (GUSTAFSSON & NORMAN 1962)

The application of roentgen methods has yielded further information about the distribution of the various mineral components building up the calculi, and the crystalline nature of the different calcium salts present has been fully established. It has also been possible to prove the existence of basic calcium phosphate in small quantities in stones from one animal.

Data collected on the chemical composition of the calculi correlate well with the observed urinary excretion pattern of the rats. Determinations of the electrolytes in the urine from a small group of rats thus showed the presence of high levels of calcium and citrate (5 to 10 times the values for the conventional rats) whereas the phosphorus content was low. The occurrence of calcium citrate in the calculi is remarkable in view of its high solubility (2.1 grams per 1 000 ml water at 30°C) (CHATTERJEE & DAHR 1924) compared to that of other calcium salts present in the calculi (calcium oxalate and apatite).

The urinary concentrations of calcium and citrate ions during germ free conditions are however evidently high enough to keep the salt in its solid state. The organization of the stones is in agreement with the finding that calculi disappeared during the ex germ free period and that the innermost part was then the first to dissolve (GUSTAFSSON & NORMAN 1962).

## SUMMARY

Bladder stones from germ free rats were investigated by means of microradiography and roentgen diffraction. The calculi were found to be composed of three different calcium salts: calcium citrate hexahydrate, calcium oxalate dihydrate and basic calcium phosphate. The proportions of these compounds and their local distribution within the stones were determined.

## ZUSAMMENFASSUNG

Blasensteine von infektionsfreien Ratten wurden mit Hilfe von Mikroradiographie und Röntgendiffraktion untersucht. Es wurde gefunden, dass die Steine aus drei Kalksalzen zusammengesetzt waren: Calciumcitrat hexahydrat, Calciumoxalat-dihydrat und Calciumphosphat. Der proportionale Anteil jedes Salzes sowie deren Verteilung innerhalb des Steines werden angegeben.

## RÉSUMÉ

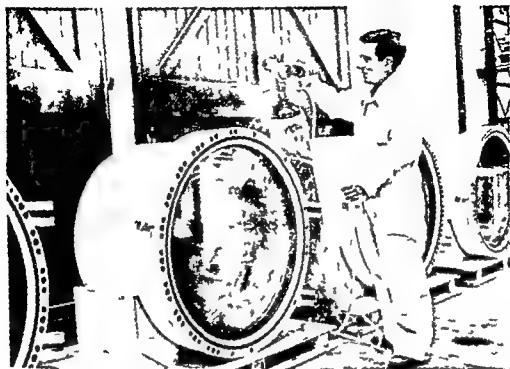
Les auteurs ont étudié en microradiographie et en diffraction de rayons roentgen des calculs vésicaux provenant de rats exempts de germes. Ils ont constaté que ces calculs sont composés de trois sels de calcium différents: le citrate de calcium hexahydrate, l'oxalate de calcium dihydrate et le phosphate basique de calcium. Ils ont déterminé les proportions de ces composés et la localisation de leur répartition dans les calculs.



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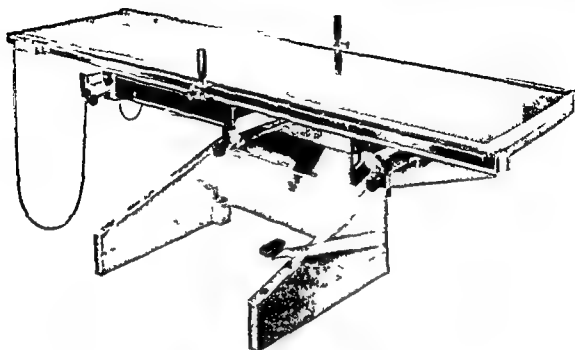
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## COSTS IN DEEP THERAPY OF A 1 r TUMOUR DOSE WITH VARIOUS RADIATION SOURCES

by

HANS LUDWIG KELLER

The practice of medicine takes its origin from motives of charity usually without regard to material considerations. But in the choice of the means the physician is necessarily bound to economic considerations. This applies particularly to the employment of larger technical resources as, for example, costly apparatus. Radiotherapy is a good example.

The product, in an economic sense, is usually equivalent to the financial expenditure. The latter consists in the outlay for the provision of treatment rooms, the purchase cost of irradiation apparatus, running costs for electricity and water, value depreciation of radiation sources and remunerations to the medical personnel.

A synopsis of the initial expenditure, financial outlay, running costs and medical salaries is shown in Table 1.

1. We have ascertained the outlay for construction of treatment rooms including the necessary radiation cubicles and accessory rooms such as reception room, physician's room, office, and lavatories. A life span of 25 years has been calculated for the rooms of primary importance and accordingly an annual

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Table I

*Financial expenditure using various radiation treatment arrangements (all the figures ex*

	200 kV 20 mA HVL 1 mm Cu	300 kV 12 mA HVL 1 mm Cu	300 kV 12 mA HVL 4 mm Cu	Cs 2 000 curie beam moving in all di- rections	Co 60 1000 curie radiation in a fixed plane	Co 60 2 000 curie radiation in a fixed plane
<i>Calculated building expenses</i>						
Treatment room						
Surrounding space in m	125	133	133	275	900	200
Costs for 1 m surrounding space	30	37 50	37 50	50	50	50
Initial cost of treatment room	3 750	5 000	5 000	13 750	10 000	10 000
Side rooms	5 000	5 000	5 000	5 000	5 000	5 000
Total building expenses without special installations	8 750	10 000	10 000	13 750	16 250	16 250
<i>Initial costs of</i>						
Apparatus and moving field treatment unit	17 500	21 250	21 250	20 000	29 000	29 000
Radiation source				2 500	5 000	10 000
Treatment table				2 500	2 500	2 500
Total initial costs without transport and custom fees	17 500	21 250	21 250	25 000	36 500	41 500
<i>Capital service per year</i>						
Building costs						
Amortization 4 °	350	400	400	750	600	650
Interest 5 °	435	500	500	937 50	825	825
Apparatus						
Amortization 10	1 750	2 125	2 125	2 250	3 150	3 150
Interest 5	875	1 062 50	1 062 50	1 250	1 875	2 075
Wear of radiation source per year				250	1 000	2 000
Rent of area and expenses for heating and lighting per year	500	500	500	500	500	500
Total capital service per year repairs included	4 250	5 000	5 000	6 250	8 500	10 000
<i>Operational costs</i>						
Tube wear expenses for electricity and cooling water per hour of radiation	1 dollar 13 cents	1 dollar 25 cents	1 dollar 25 cents			
Annual expenditure at maximum yearly performance	1 425	1 000	1 750			
Annual salaries of staff	8 500	8 500	8 500	8 500	8 500	8 500
Total sum of annual expenditure operational costs at the theoretically possible maximum yearly performance	14 175	14 500	15 250	14 750	17 000	18 500

Table 1 (cont.)

Except the first line figures represent the space required correspond to dollars and cents)

Co 60 2000 curie ra- diation beam moving in all di- rections	Co 60 4000 curie ra- diation beam moving in all di- rections	Co 60 8000 curie ra- diation beam moving in all di- rections	18 MeV betatron roentgen rays	18 MeV betatron fast elec- trons	35 MeV betatron roentgen rays		35 MeV betatron fast elec- trons	Linear accelerator 4.3 MeV (SL 48)	
					Without field homo- geneisa- tion	With field homo- geneisa- tion		roentgen rays	fast elec- trons (theoretically)
400	400	400	400	450	500	500	500	500	500
50	50	50	55	50	75	75	75	75	75
20 000	20 000	20 000	25 000	25 000	37 500	37 500	37 500	37 500	37 500
6250	6250	6250	7 500	7 500	7 500	7 500	7 500	7 500	7 500
26 250	26 250	26 250	32 500	37 500	45 000	45 000	45 000	45 000	45 000
42 500	47 500	47 500	112 500	112 500	185 500	185 500	185 500	150 000	150 000
10 000	20 000	40 000							
2 500	2 500	2 500							
55 000	70 000	90 000	112 500	112 500	185 500	185 500	185 500	150 000	150 000
1 050	1 050	1 050	1 300	1 300	1 550	1 550	1 550	1 550	1 550
1 312.50	1 312.40	1 312.50	1 625	1 625	2 250	2 250	2 250	2 250	2 250
4 500	5 000	5 000	11 250	11 250	18 550	18 550	18 550	15 000	15 000
2 750	3 500	4 500	5 625	5 625	9 250	9 250	9 250	7 500	7 500
2 000	4 000	8 000							
500	500	500	500	500	500	500	500	500	500
12 500	15 750	20 375	21 250	21 250	33 750	33 750	33 750	28 750	28 750
			11 250 \$	11 250 \$	3 750 \$	3 750 \$	3 750 \$	1 750 \$	1 750 \$
			10 000	3 750	3 250	4 500	875	1 125	1 125
8 500	8 500	8 500	10 500	10 500	10 500	10 500	10 500	10 500	10 500
					Technical staff			2 000	2 000
21 000	24 250	8	41 0	5 00	47 500	48 750	45 000	42 375	42 375

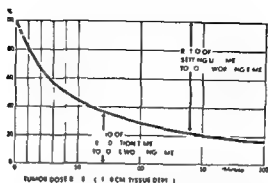


Fig 1 Relationship of preparation time to irradiation time depending upon the tumour dose rate single tumour doses of 250 r in 10 cm tissue depth preparation time 6.3 min

depreciation in value of 4 %. Interest at 5 % on the initial funds was also taken into consideration. The internal area of the treatment room was calculated at 25 m<sup>2</sup>.

2 For the radiation sources and irradiation apparatus an average life of 10 years and therefore an annual depreciation of 10 %, and an annual interest at 5 % on the purchase price, were selected.

3 The running costs, i.e. costs of electricity (about 2.5 cents per kilowatt) and cooling water (about 12 cents per m<sup>3</sup>), as well as wear and tear of radiation sources are about proportionally dependent on the number of working hours. An overall sum for recurring costs, such as for heating and lighting of the rooms, also has to be included. The expenditures for writing material, forms, and patient statistics may apparently be neglected.

4 Essential items are the salaries and wages of the treatment personnel. For the operation of a full time irradiation unit the costs were estimated as follows:

Annual expenditure for 1 assistant radiologist	\$ 4 000
Annual combined expenditure for 1 1/2 technical assistants	\$ 3 500
Share of typist 1/2 salary per annum	\$ 600
Share of cleaning 1/3 salary per annum	\$ 400

In all \$ 8 500

These expenses for personnel are about the same with fully worked apparatus for deep therapy of conventional construction and with radioactive isotopes as radiation source. In the case of various particle accelerators a further amount must be added for technical personnel.

A physicist does not appear to be indispensable, but for the linear accelerators and the betatrons it is necessary to employ well trained personnel. Accordingly, for such medical personnel an annual expenditure of \$ 10 500 in toto was arrived at.

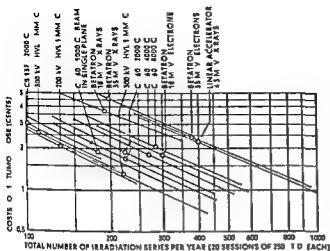


Fig 11 Comparison of the yearly performance and costs of 1 r tumour dose using various sources of radiation. The continuous curves show the range of yearly performance from cost standpoint between 25% and 75% fulfilment of the maximum yearly performance theoretically possible. A circle on the curve marks a 40% fulfilment.

The roentgen tumour dose corresponds economically to the means produced by the costs. Health insurance companies in various countries take the superficial dose as the basis for calculation of the fee for deep therapy but this is apt not to compensate for the best qualitative results. For example, deep therapy with low energy radiation must obviously be in a different category from treatment with ultra hard radiation. In the present consideration it is therefore the dose applied to the tumour that is made the focus of the economic evaluation.

The number of working hours is on the whole a constant. The working year consists of about 50 weeks each of 40 working hours and therefore amounts to 2000 working hours. In this period of time only a certain number of treatments can be carried out. The time allotted to the treatment of each individual may be divided into a so called preparation time and the treatment time itself. In the preparation time the patient is brought into the room undressed, positioned upon the table and the treatment field set up. After the treatment he is dressed and taken from the room. It would appear that the preparation time is a little over 6 minutes. Our average value with always the same medical personnel is generally constant. On the other hand the treatment time depends upon the tumour dose rate of the apparatus used.

The relation between preparation time and treatment time is therefore equivalent to the relation between a constant and a variable quantity. It is illustrated in the first graph (Fig 1) with the percentage proportion of treatment time to the total working time on the ordinate and the various tumour dose rates taken at an average depth of 10 cm on the abscissa. It will be seen that



Table 2

*Comparison of accomplished tumour doses by various radiation units*

	200 kV 20 mA HVL 1 mm Cu	300 kV 12 mA HVL 1 mm Cu	300 kV 12 mA HVL 4 mm Cu	<sup>60</sup> Co 2000 C beam moving in all di- rections	<sup>60</sup> Co 1000 radiation  At com- mencing activity
Free air dose (r/min) (50 cm focus to chamber distance)	70	200	45	30	78
Relative depth dose in      of free air dose for roentgen rays in 10 cm tissue depth for fast electrons according to energy	30 %	30	38	43	49 %
Tumour dose rate for roentgen rays in 10 cm tissue depth for fast electrons at the dose maximum (no values given)	210 r/min	60 r/min	17 r/min	13 r/min	38 r/min
Hours of radiation per year of 2000 working hours	1300 hours	800 hours	1360 hours	1540 hours	1000 hours
Tumour dose at maximum yearly per- formance in 10 r	164	29	14	12	23
Treatment series per year $\Delta 20 \times 250$ r tumour dose	328	580	280	240	460
Single treatments per year $\Delta 250$ r tumour dose	6560	11600	5600	4800	9200
Single treatments $\Delta 250$ r per working day (1 year = 260 working days)	25	44.5	21.5	18.5	35.5
Costs of 1 r tumour dose at 100 % utili- zation of the theoretically possible maxi- mum yearly performance (Amer. cents)	0.875	0.5	1.1	1.23	0.7
Costs of 1 r tumour dose at 40 % utili- zation of the theoretically possible maxi- mum yearly performance (Amer. cents)	2.1	1.2	2.65	2.95	1.68

at a tumour dose rate of about 38 r/min, the preparation time is equal to the irradiation time. At smaller dose rates the treatment time predominates, and for larger dose rates the preparation time is greater. It therefore follows that in a working year of 2000 hours at high dose rates a relatively short irradiation time is required compared with a relatively long time with small tumour dose rates. This may be exemplified as follows:

At a tumour dose rate of 62 r/min the working year consists of 800 irradiation

Table 2 (cont.)

(See also pp 376-377 for horizontal continuation of table)

C fixed plane	Co 2000 C fixed radiation plane		Co 2000 C beam moving in all directions		Co 4000 C beam moving in all directions	
	By half life	At commencing activity	By half life	At commencing activity	By half life	At commencing activity
110	144	72	144	72	260	130
49	49	49	49	49	49	49
19 r/min	70 r/min	35 r/min	70 r/min	35 r/min	128 r/min	64 r/min
1340 hours	740 hours	1040 hours	740 hours	1040 hours	480 hours	760 hours
153	31	22	31	22	37	29
307	620	440	620	440	740	590
6120	12400	8800	12400	8800	14800	11800
24	48	34	48	34	47	40
112	06	083	060	090	081	083
27	144	20	156	227	158	20

hours, whereas at a tumour dose rate of 17 r/min the working year is increased to 1360 irradiation hours. Consequently in order to achieve twice the number of treatments during a working year for example it is not sufficient to double the tumour dose rate it must be increased to more than 4 times its value. Moreover, it is clear that each treatment unit can only achieve a certain number of tumour series per year, and this depends upon the average tumour dose rate (See Table 2).

Table 2 (cont.)

	<sup>60</sup> Co 8000 C beam moving in all directions		10 MeV betatron roentgen rays	
	At com- mencing activity	By half life	Without field homo- genisation	With field homogeni- sation
Free air dose (r/min) (50 cm focus-to-chamber distance)	500	250	80	65
Relative depth-dose in % of free air dose for roentgen rays in 10 cm tissue depth for fast electrons according to energy	49 *	49 %	63 *	63
Tumour dose rate for roentgen rays in 10 cm tissue depth for fast electrons at the dose maximum (no values given)	196 r/min	98 r/min	50 r/min	35 r/min
Hours of radiation per year of 2000 working hours	200 hours	280 hours	880 hours	1080 hours
Tumour dose at maximum yearly per- formance in 10 r	40	28	265	23
Treatment series per year & 20 x 250 r tumour dose	800	560	530	460
Single treatments per year & 250 r tumour dose	16000	14000	10600	9200
Single treatments & 250 r per working day (1 year = 260 working days)	80	70	41	35
Costs of 1 r tumour dose at 100 % utili- zation of the theoretically possible maxi- mum yearly performance (Amer cents)	0.73	0.93	1.58	1.8
Costs of 1 r tumour dose at 40 % utili- zation of the theoretically possible maxi- mum yearly performance (Amer cents)	1.76	2.25	3.6	4.25

The cost of 1 r tumour dose may be given by a certain figure only when a fixed number of patients are treated per annum. Strictly speaking the relationship can be shown only by means of a cost performance graph (Fig. 2). This gives the costs per 1 r tumour dose in cents on the ordinate and the number of applied tumour series per annum on the abscissa. The continuous curves indicate the cost range of yearly performance between a 25 % and 75 % utilization of the theoretically possible maximum annual performance. A circle on

Table 2 (cont.)

18 MeV betatron fast electrons	30 betatron roentgen rays		30 MeV betatron fast electrons	Linear accelerator 4 to 6 MeV	
	Without field homogen- isation	With field homogen- isation		Roentgen rays	Fast electrons (theoret- ically)
300	70	40	ca 500	400	ca 500
	focus-to-chamber-distance 1 m			focus-to-chamber-distance 1 m	
ca. 100	60 °	65 °	ca. 100 °	60 °	ca 100 °
ca 250 r/min	111 r/min	26 r/min	500 r/min	ca 250 r/min	ca 500 r/min
ca. 400 hours	ca 860 hours	1 700 hours	ca 400 hours	ca 400 hours	ca 400 hours
4.5	2.6	1.88	4.8	4.8	4.8
900	570	375	ca 1 000	ca 1 000	ca. 1 000
18 000	10 400	7 500	ca 20 000	ca 20 000	ca. 20 000
69	40	29	ca 80	ca 80	ca 80
0.186	1.82	9.6	0.90	0.870	0.870
1.88	4.36	6.25	2.3	2.1	2.1

the curves marks the 40% accomplishment of the maximum yearly performance. The costs of a 1 r tumour dose at an average utilization of the efficiency of the radiation sources may thus be calculated. Modern radiation units necessitating a relatively high initial expenditure mostly compensate for this extra cost by an increase in the yearly work performance. This applies particularly to the cobalt 60 sources to the linear accelerators and to the betatrons especially if employed as electron generators. If betatrons are

Table 2 (cont.)

	$^{60}\text{Co}$ 8000 C beam moving in all directions		18 MeV betatron roentgen rays	
	At com- mencing activity	By half life	Without field homo- genisation	With field homogeni- sation
Free air dose (r/min) (50 cm focus-to-chamber-distance)	500	250	80	60
Relative depth-dose in of free air dose for roentgen rays in 10 cm tissue depth for fast electrons according to energy	49 %	49 %	63 %	63
Tumour dose rate for roentgen rays in 10 cm tissue depth for fast electrons at the dose maximum (no values given)	196 r/min	98 r/min	50 r/min	30 r/min
Hours of radiation per year of 2000 working hours	200 hours	280 hours	880 hours	1080 hours
Tumour dose at maximum yearly per- formance in 10 r	40	28	265	23
Treatment series per year at 20% tumour dose	800	560	530	460
Single treatments per year at 250 r tumour dose	16000	14000	10600	9200
Single treatments at 250 r per working day (1 year = 260 working days)	80	70	41	35
Costs of 1 r tumour dose at 100 % utili- zation of the theoretically possible maxi- mum yearly performance (Amer. cents)	0.73	0.93	1.58	1.8
Costs of 1 r tumour dose at 40 % utili- zation of the theoretically possible maxi- mum yearly performance (Amer. cents)	1.76	2.25	3.6	4.25

The cost of 1 r tumour dose may be given by a certain figure only when a fixed number of patients are treated per annum. Strictly speaking the relationship can be shown only by means of a cost performance graph (Fig. 2). This gives the costs per 1 r tumour dose in cents on the ordinate and the number of applied tumour series per annum on the abscissa. The continuous curves indicate the cost range of yearly performance between a 25 % and 70 % utilization of the theoretically possible maximum annual performance. A circle on

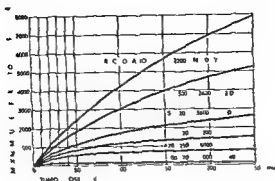


Fig 4 Theoretical maximum performance of treatment series per year (for a working year of 2000 hours) depending upon the tumour dose rate for various fractionations with biologic equivalent effect on the tumour (from ANDREWS & MORRIS)

The cost consideration in the choice of radiation technique and fractionation is of particular interest

In order to apply a tumour dose of 5000 r in single surface doses of 250 r using the stationary field and cross fire technique according to the choice of radiation and the various relative depth doses 66 to 31 single treatments are required, as opposed to 20 treatments with moving field therapy. To obtain the same tumour dose therefore, the stationary field method leads to higher fractionation.

Such a fractionation involves a considerable average reduction of 0.66 times the yearly performance, as may be seen from Fig 4. Providing there is a sufficiently high number of available cases this results in a 50% cost increase for a 1 r tumour dose. Apart from the clinical point of view economic considerations therefore become critical factors in the argument that moving field therapy is to be preferred to the stationary field technique.

## SUMMARY

The annual expenses of radiation deep therapy (cost of buildings and plant and running expenses and salaries of staff) are considered in relation to the possible tumour dose rate (at 10 cm tissue depth) with various types of apparatus. These would appear to vary to a marked degree in various centres. Tables are shown from which variations according to local circumstances may be derived. It is evident that the relatively high cost of elaborate apparatus may often be offset by the large number of cases possible to treat.

## ZUSAMMENFASSUNG

Es wird der Jahresaufwand für die Strahlentiefentherapie (Kosten für Gebäude, Bestrahlungseinrichtungen, Betriebsmittel und Personal) gegenübergestellt der möglichen Dosisleistung am Herd (in 10 cm Gewebetiefe) pro Jahr bei verschiedenen Tiefentherapiegeräten. Die Ar-

beit ist sich bewußt, dass in der Welt die Kosten sehr verschieden sind. Es werden daher Tabellen gezeigt, die nach den lokalen Verhältnissen variiert werden können. Bei Apparaturen mit hohem Anschaffungspreis wird häufig infolge der wesentlich höheren Dosisleistung ein viel grösseres Patientengut bewältigt.

## RÉSUMÉ

L'auteur a déterminé d'une part le coût annuel de la thérapie profonde par les radiations (coût des bâtiments et des appareils d'irradiation, frais de fonctionnement et salaires) et d'autre part la dose à la tumeur (à 10 cm de profondeur) que peuvent émettre annuellement divers types d'appareillages de thérapie profonde. Les frais peuvent varier beaucoup d'un pays à l'autre. L'auteur publie des tableaux que l'on peut adapter à ces facteurs locaux. Souvent les appareils dont le prix d'achat est élevé ont une capacité de fonctionnement annuel notablement plus grande permettant de traiter beaucoup plus de malades.

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## BOOK REVIEWS

**IONIZING RADIATION: AN OLD HAZARD IN A NEW ERA.** By George Tievsky 154 pages 63 illustrations and 5 tables Charles C Thomas Springfield Ill 1962 Price \$ 8

The physical radiobiologic and genetical background to the understanding of various kinds of radiation hazards are first presented in a simplified and sometimes not too accurate manner. In the two chapters on fluoroscopy and radiography the author stresses the importance to limit as far as possible without jeopardizing the diagnostic results the radiation doses received by patients and personnel. He gives the more important rules to follow for this end. These rules should already be well known and applied. It is to be hoped by all radiologists but surgeons and others using roentgen radiation and without special training in radiology should study them closely. The author rightly advises non radiologists to refrain from more specialized and difficult roentgen examinations because of lack of experience they will usually inflict unnecessarily high doses on their patients and themselves and with inferior diagnostic result. There is no special chapter on radiotherapy.

The irradiation of human beings in general by natural radioactivity and by radioactive fall out is then discussed and some comparisons of magnitudes are presented in order to retain a sense of proportions. Some figures are contained in an appendix by G M Dunning. Legal considerations are stressed such as the difficulty in many cases of deciding whether a workman's compensation claim for radiation injury is warranted as well as the impossibility of founding a future policy in all questions of radiation protection solely on scientific facts. A judgment of values is also necessary to ensure that the positive consequences of a proposed policy weigh over the negative ones. Finally some information is given on national and international bodies considering radiation hazards on Handbooks of the National Bureau of Standards and a glossary of terms is presented.

In short the book constitutes a popular and readable presentation of a subject of great topical interest although parts of it should be taken with a grain of salt. A study of the references quoted should be helpful in this respect.

*Sven Benner*

**DIE WIRBELSAULE IN DIAGNOSTIK UND THERAPIE.** Verhandlungen der 2. Arbeitstagung der Gesellschaft für Wirbelsäulenforschung 1961 in Frankfurt am Main 208 Seiten 79 Abbildungen Hippokrates-Verlag Stuttgart 1962. Price 39 DM

This book reports on 35 congress papers. Some of the papers dealing with radiography of the vertebral arteries performed on cadavers in the course of which the blood flow at different rotations of the spine was experimentally studied are of particular interest to radiologists. The clinical significance of this mechanical influence is discussed in the light of similar studies in patients.

The lectures are of general and theoretical interest but they do not from the purely radiologic viewpoint provide much new information.

*Folke Knutsson*



**I INTERNATIONALER KONGRESS FÜR MEDIZINISCHE PHOTOGRAPHIE UND KINEMATOGRAFIE**  
Herausgegeben von H. Orbach 362 Seiten und 275 Abbildungen Georg Thieme Stuttgart  
1962 Price DM

The first International Congress of Medical Photography and Cinematography was held at Dusseldorf in September 1960 the transactions have now been beautifully printed in a handy volume containing about 140 papers. Many subjects from the wide field of photography are of interest to a radiologist although some of them will be well known from recent radiologic meetings. Some technical papers particularly those on modern roentgen films and their properties and on processing machines will also prove of value. Parts of the papers on image quality obtained with the image amplifier and on problems connected with television and cinefluorography memory tubes and the microroentgen technique have been published previously.

Of probably less account to the radiologist are the communications on endoscopic ophthalmologic dental orthopedic and surgical photography Fluorescence photography (for skin diseases) and electron microscopy are also dealt with and general medical photography educational films and the standardization of photography in hospitals are discussed. Cinematography in different connections is comprehensively covered.

The comments in the accompanying discussions at least those that have been published are surprisingly few. The reviewer regrets that the author of the paper on the possibilities of reducing dosage by increasing the development temperature seems to have overlooked certain important elementary physical facts.

*Ole Mattsson*

**STRAHLENSCHUTZ IN FORSCHUNG UND PRAXIS Band I** Jahrbuch der Vereinigung deutscher Strahlenschutzärzte Herausgegeben von H. J. Melching 252 Seiten 93 Abbildungen und 31 Tabellen Rombach Freiburg im Breisgau 1962 Price DM 39

Lectures covering a survey of selected topics during a radiation protection course to German physicians in January 1961 are collected in this book. The interests of those actually working with radiation of those exposed as patients during radiologic examinations and treatments and of third parties are considered. The report of H. HOLTHUSEN on the extensive investigation of patient doses in Hamburg in which about 14 million examinations and treatments are analyzed is of special interest. HOLTHUSEN and other authors stress the importance of improving methods in common use and the possibility substantially to reduce patient doses without sacrificing the medical value of examinations.

Other papers describe various forms of radiation injury and the treatment in such cases as well as waste disposal in atomic energy and medical isotope work. The German legal aspects of radiation protection appear to be of limited value to readers in other countries although questions of general interest are also discussed in these communications e.g. the difficulty or impossibility of proving in a given case the causal relationship between irradiation and injury especially when the latter is delayed. This naturally limits the chance of the injured party obtaining compensation from the responsible authority.

*Sten Benner*

**WHOLE BODY COUNTING** Proceedings of a symposium held by the International Atomic Energy Agency Vienna 12—16 June 1961 535 pages International Atomic Energy Agency Vienna 1962 Price 3 £ (in North America 10 00 \$)

The measurement of low level radio-activity in the human body is a field of study requiring considerable skill and care in the design of apparatus in the performance of measurements and in the interpretation of the results. If these conditions are fulfilled valuable information on radio-active fall-out distribution and metabolism may be obtained. It is further possible to perform several diagnostic radio-isotope studies with a much smaller quantity of radio-activity than in ordinary methods or to follow the excretion of a given dose over a longer period of time. The measurement of natural radio-activity in the body is also often of clinical interest.

A debt of gratitude is therefore owed to the International Atomic Energy Agency for convening a meeting of prominent scientists from several countries and for publishing the proceedings in the present volume containing 33 papers mostly in English but 5 of them in French. Various types of detectors, calibration methods, typical measurement facilities and data processing techniques are described. Some devices for measuring the activity in part of the body or for studying the activity distribution are also mentioned.

Certain papers concern the measurement of natural radio-activity from which potassium content and lean body mass may be estimated, others which cannot be reviewed in detail give several examples of the advantages accruing from the use of low level counting methods for various diagnostic tests.

The book should be of great interest to all workers in the field and its value is enhanced by the summaries of discussions which give much useful supplementary information.

*Sven Benner*

**MOLECULAR BIOPHYSICS** By Richard B. Setlow and Ernest C. Pollard 545 pages 258 illustrations and 52 tables Pergamon Press Oxford 1962 Price 84 Sh

This book gives an account of the various physical and chemical methods in use for studying the structure and properties of biologically important complicated organic molecules (diffusion, sedimentation, birefringence, absorption spectra, roentgen ray diffraction, electron spin resonance). It further reviews cellular biology in general and commonly used methods such as light and electron microscopy, isotopic tracer methods, radiation effects on viruses, enzymes, cells and especially chromosomes. One chapter gives applications in muscle, nerve and eye physiology. Most of the chapters end by a number of problems for the reader.

The book contains a wealth of factual matter and interesting discussions on important topics especially from the physicist's point of view. It does not always provide easy reading but is well worth a thorough study by anyone who wants to penetrate the problems dealt with or who is already active in the field. The chapters dealing with radiation effects and isotopic tracer methods would seem to be of greatest interest to the readers of this Journal.

*Sven Benner*

Einführung in die Messtechnik der Kernstrahlung und die Anwendung der Radioisotope 2. Auflage Herausgegeben von H. Fassbender 420 Seiten 244 Abbildungen und 26 Tabellen. Georg Thieme, Stuttgart 1962 Price 49.50 DM

The first edition of this book was described by the present reviewer as being probably of more interest to technical than to medical readers. The second edition has been considerably enlarged and is the work of specialists in the various fields and now no longer written by one author. Medical questions are however still treated relatively briefly, emphasis being placed on radiation measurements and the design of the necessary instruments. The book seems to be of particular interest to instrument designers and those concerned with the technical uses of radioisotopes.

*Sten Benner*

## AUTORADIOGRAPHY OF VARIOUS RAT TISSUES AFTER THE ADMINISTRATION OF BISMUTH 210

by

C J H VAN DEN BROEK

The use of  $^{210}\text{Bi}$  as a radiation source in the detection and therapy of neoplastic diseases has been investigated by VAN DER WERFF (22, 23). In the course of this work it was thought desirable to collect more detailed information on the distribution of bismuth in various organs and tissues. Autoradiography is the usual method of choice for this kind of information. However  $^{210}\text{Bi}$  being a pure  $\gamma$  emitter is unsuitable for anything but the roughest localization. Thus VAN DER WERFF & HAANEN (24) who used  $^{210}\text{Bi}$  absorbed on coal particles and injected this into leucemic patients obtained only a vague contact autoradiogram of its accumulation in a lymph node.

Bismuth 210 on the other hand decays with a half life of 50 days with emission of 1.17 MeV  $\beta$  rays into  $^{210}\text{Po}$  this in turn decays with a half life of 140 days with emission of both  $\alpha$  (5.3 MeV) and  $\gamma$  rays into stable  $^{206}\text{Pb}$ . Whereas the mean  $\beta$  energy of  $^{210}\text{Bi}$  is rather high for accurate localization in autoradiograms the  $\alpha$  particles of polonium produce short straight tracks in a photographic emulsion which can be traced down even to individual cells. A sharp localization of bismuth is therefore possible by injecting a preparation of freshly isolated  $^{210}\text{Bi}$  into a test animal fixing its tissues after a time interval.

From the Department of Histology, Faculty of Medicine, University of Utrecht, the Netherlands. Submitted for publication III January 1963.

short in comparison with the half life of  $^{210}\text{Bi}$ , storing the dehydrated tissues in paraffin blocks for some 4 to 5 of these half lives and studying in autoradiograms the distribution of the  $\alpha$  tracks originating from the  $^{210}\text{Po}$  that has developed from practically all the  $^{210}\text{Bi}$  during the storage interval. LACASSAGNE & FOUGAULD (6) in the early thirties demonstrated the presence of bismuth in various organs by this method and later KAHN (5) recorded its presence in tumours. Since then the autoradiographic technique has been markedly improved (ref. 20) and its resolution brought down to the cellular level.

The method has the disadvantage that a time interval between the isolation of  $^{210}\text{Bi}$  and its administration to the animal, and between the latter and the fixation of the tissues, is unavoidable. Whereas the first period can be reduced to a minimum the second is inherent to the experiment. It was thought, however, that the 13 per cent of  $^{210}\text{Bi}$  that turned into  $^{210}\text{Po}$  within the first 24 hours after administration would not seriously impair a demonstration of a possibly specific accumulation of bismuth.

In the present experiment the preparation and injection of  $^{210}\text{Bi}$ , as well as all work on the tissues up to their embedding in paraffin were carried out at the St. Canisius Hospital, Nijmegen, Holland under the supervision of Mr. VAN DER WERFF upon the request of whom the preparation and evaluation of the autoradiograms were carried out by the present author.

*Materials and Methods*  $^{210}\text{Bi}$ , as a  $\text{BiCl}_3$  solution, was obtained from Philips Duphar, Amsterdam. The vena saphena of 5 ordinary white rats of approximately 200 g bodyweight was injected with 1 ml neutral saline prepared to contain 0.1, 0.3, 1.3, and 10  $\mu\text{C}$  respectively, these doses correspond with the range from tracer dose to therapeutic dose in man. The 5 animals together with a control were killed after 24 hours, and the liver, lung, kidney, spleen and bone marrow (sternum) were immediately fixed in 10% formaldehyde solution and embedded in paraffin wax according to usual practice. The exact time interval between the preparation of the batch of  $^{210}\text{Bi}$  and the injection of the animals was unfortunately not registered so that the injected solution contained more than the unavoidable minimum of polonium. Although this would undoubtedly diminish the exactitude, it was thought that some of the results were sufficiently clear to warrant this report, the more so as the said time interval was reported to be considerably shorter than the half life of bismuth and hence the contamination by polonium considerably less than 50 per cent (VAN DER WERFF).

Between 20 and 35 days after fixation, 3  $\mu$  and 7  $\mu$  sections were prepared and autoradiograms obtained by the application of Kodak AR 10 stripping film in the usual manner (ref. 1, 20). The exposure time for most preparations varied between 3 and 12 weeks; for bone marrow this was extended to 22 weeks because of the rather low radioactivity and small available tissue areas.

Table 1

*Radioactivities of various tissues as percentages of the highest radioactivity*

Injection prepared to contain	0.1 $\mu\text{C}$	0.3 $\mu\text{C}$	1 $\mu\text{C}$	3 $\mu\text{C}$	10 $\mu\text{C}$	Mean
Kidney tubuli	100	100	100	100	100	100
glomeruli	51.7	87.8	111.2	79.4	61.7	79.0
Spleen red pulp	34.2	55.6	38.8	48.5	30.6	41.5
white pulp	26.6	37.5	36.2	36.3	25.0	32.3
Liver periportal area	18.6	30.2	18.6	33.9	17.9	23.8
parenchyma	17.1	31.9	15.6	18.5	19.9	20.6
vena centralis	22.9	23.4	13.6	14.1	14.8	17.7
Bone marrow	11.4	19.2	14.6	11.6	13.3	14.0
Lung parenchyma	6.0	22.9	11.6	10.8	10.3	12.3
Kidney medulla	13.0	13.6	8.3	6.1	6.0	9.4

Notwithstanding its limited thickness of  $5\mu$ , the stripping film, after development in Kodak D19b at 18°C for 5 min and fixation, showed very clear tracks which were subsequently evaluated in the following two ways.

1 Homogeneous tissue areas were sought in autoradiograms made from  $7\mu$  sections stained with methyl green and pyronine and showing suitable track densities; their surfaces were measured from camera lucida drawings and the number of tracks counted. After due corrections for radioactive decay, exposure time and background (negligible for tracks) comparable figures were arrived at for the number of tracks per  $10\,000\mu^2$  tissue area per unit exposure time. Figures, derived from preparations from one tissue after different times of exposure, generally agreed within 20 to 30 per cent with some exceptions in cases of low track density.

2 Similar homogeneous tissue areas were sought and systematically searched with an oil immersion objective in autoradiograms from  $3\mu$  sections stained with Mayer's hemalum. The origin of the type of cell was registered in at least 200 tracks. The track distribution thus found was then compared with a chance distribution obtained by registering the cells on which a black dot mounted in the microscope ocular fell in at least 200 chance positions of the preparation (point hit method).

## Results

1 *Quantitative* All tissues studied gave a measurable number of tracks in the autoradiograms but in all animals striking variations in track density between tissues or tissue components were observed. Moreover the relative radioactivities of the various tissue components were found to be essentially similar for all doses administered. These relative radioactivities expressed as

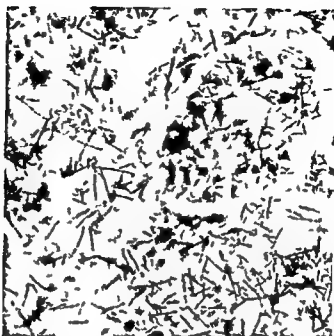


Fig. 1. a track autoradiogram of rat renal cortex fixed 24 hrs after administration of  $10 \mu\text{C}$   $\text{Ba}^{133}$  chloride. Very high track density over proximal convoluted tubules, less in glomerulus.

percentages of the track density of the tissue component with the highest incorporation: i.e. renal tubules (with one minor exception) are presented in Table 1. Tissue components are arranged in the table in the order of decreasing radioactivity, and the similarity of this order permits its expression in the mean percentages given in the last column.

It is apparent from these figures that 24 hours after injection of any dose between 0.1 and  $10 \mu\text{C}$  there is a marked concentration of the isotope(s) in the renal tubuli and only little less in the glomeruli (in the latter supposedly in the process of excretion). The renal cortex as a whole always contains about ten times as much isotope as the renal medulla. Isotope concentration in the spleen, though still prominent, is much lower, and the radioactivity of the red pulp is consistently somewhat higher than that of the white pulp. It is surprising to find no significant difference between the parenchyma and the periportal areas of the liver. The track numbers for the venae centrales apply only to tracks evident in the lumina of these vessels, inside as well as outside the blood cells. It is obvious, especially when comparison is made with the figures for the renal medulla, that the liver accumulates the isotope, albeit in a lesser degree than the renal cortex. This accumulation stands out more clearly when other tissues are also taken into account. Incidental but less complete countings performed for muscle and bone reveal a track density in

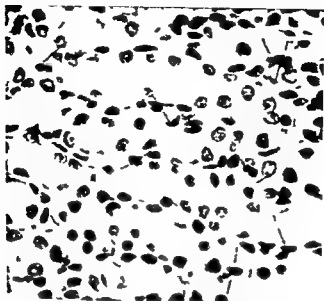


Fig. 2. Autoradiogram of rat renal medulla fixed 24 hrs after administration of  $10\ \mu\text{C}$   $^{210}\text{Po}$  chloride. Same exposure time as in fig. 1 hence track densities comparable.

these tissues of the same order of magnitude as in the renal medulla and thus noticeably weaker than in the liver. The approximation of the counts for the hepatic parenchyma, periportal areas and venae centrales may indicate that 24 hours after injection there is still a marked transport of isotope in the liver.

The figures for the lung are much lower than those for the liver but as only a part of the pulmonary areas evaluated represents tissue proper the track count for the latter may well be in the same order of magnitude as that for the liver. The low figures for bone marrow are unexpected especially in relation to those for the spleen. These figures have however been checked in a fair number of additional preparations.

The ratios of tissue radioactivity are given for each tenfold increase in dose in Table 2. With some exceptions which must be ascribed to the low track numbers obtained from the  $0.1\ \mu\text{C}$  dose, most of these ratios are seen to lie between 5 and 7. Hence for all tissues the increase in radioactivity is approximately proportional to the injected dose. Notwithstanding the apparent accumulation of isotope in some organs, radioactivity in most tissues increases 5 to 7 times for each tenfold increase in dose over the entire range from  $0.1$  to  $10\ \mu\text{C}$ .

As far as deviations from this general rule can be observed it might seem that the ratios are lowest for the less radioactive tissues. This would imply



Table 2

*Track count ratios for a 10 l increase in dose*

Dose ratio	1 0 0 1	3 0 0 3	1 0 0 1 0	Mean
<i>Kidney tubuli</i>	59	99	58	72
glomeruli	126	89	34	83
<i>Spleen red pulp</i>	66	86	46	66
white pulp	80	95	40	72
<i>Liver periportal area</i>	58	110	56	75
parenchyma	53	57	74	61
vena centralis	35	59	63	52
<i>Bone marrow</i>	75	59	53	62
<i>Lung parenchyma</i>	113	47	52	71
<i>Kidney medulla</i>	37	45	42	41
Mean	70	75	52	66

that the capacity of the actively accumulating tissues has not been overloaded by the higher doses of isotope.

Finally, as all counts were derived from tissue sections of identical thickness, the relative radioactivities given in Table 1 may also be regarded as the relative isotope dose per unit volume of these tissues. They may assist in furnishing an idea of the radiation damage to be expected in these tissues during the first day after injection of  $^{214}\text{Bi}$  chloride.

2 *Qualitative* The qualitative evaluation of the autoradiograms, for which over 5 000 tracks were traced down to individual cells, showed that the track distribution in the great majority of cases coincided closely with a random distribution recorded by the point hit method.

The cells of the proximal convoluted tubules in the renal cortex only (see Fig. 1) had an accumulation of tracks far in excess of the random distribution. It is predominantly by these cells that the isotope or isotopes are accumulated within the first 24 hours after injection. The track density in the distal convoluted tubules was judged to be only little in excess of that in the renal medulla where it was very low (see Fig. 2). The far more numerous tracks in the glomeruli again showed an essentially random distribution.

Seven per cent of the tracks in the spleen of two of the five animals were traced down to macrophages against 3 per cent random hits. Owing to the relative scarcity of these cells no more than 96 tracks have been attributed to them, but this number seems sufficient to explain them as a sign of some accumulation by these cells.

No significant accumulation could be detected in the Kupffer cells of the liver. Conversely, if these cells should have accumulated isotope to any marked



Fig. 3. Autoradiogram of rat lung fixed 24 hrs after administration of  $10 \mu\text{Ci}$   $^{210}\text{Bi}$  chloride. Tracks are present likewise over lung parenchyma and arterial media.

degree, it would certainly have been noted amidst the rather low overall track density.

Tracks over various tissue components of the lung are depicted in Fig. 3 to illustrate the random distribution in other tissues.

### Discussion

Neither the distribution of tracks at the organ level nor that at the cellular level show any variations corresponding with the 1:100 variation in the administered dose. This would mean that even the largest dose (equivalent to a therapeutic dose in human subjects, as previously mentioned) is not large enough to disturb the distribution to any marked degree within the first 24 hours after injection. It remains of course to be seen whether the influence of an isotope dose would (quite aside from a difference in radiation damage) become noticeable at longer intervals.

There seems to be some contradiction between the qualitative and the quantitative results described above. The former clearly point to a specific accumulation of isotope by some tissues, especially the renal cortex and spleen, but in the latter such specificity is much less marked at the cellular level, where only the proximal tubules of the kidney and less definitely the macrophages of the spleen display signs of accumulation.

Table 3

*Comparison of relative radioactivities in rat and mouse organs 24 hours after the administration of radioactive Bi in aqueous solution in various experiments*

Authors	Ref	Compound	Animal	Kidney	Spleen	Liver	Lung	Bone marrow
LACASSAGNE	16	$^{210}\text{Bi}$	Rat	100	0.5	1.5	0.5	—
	Table 2	nitrate		$\wedge$	$>$	$>$	$>$	
LACASSAGNE	17	$^{210}\text{Bi}$	Mouse*	100	4.1	8.2	4.1	—
	Table 2	nitrate		=	$<$	$>$	=	
PASSALACQUA	17	$^{210}\text{Bi}$	Rat*	100	20	5	—	25
	Table 3	nitrate		$<$	$>$	$<$		$<$
PASSALACQUA & KOCH	19	$^{210}\text{Bi}$	Rat*	100	2	4	■	0
	Table 3	nitrate		$<$	$<$	$<$	$<$	=
MATTHEWS**	15	$^{210}\text{Bi}$	Rat	100	1.4	2.2	1.0	—
	Table 2	nitrate		$>$	$>$	$>$	=	
VAN DEN BROEK	Present paper	$^{210}\text{Bi}$ chloride	Rat	100	54	22	17	21

\* Control animals: animals bearing tumours omitted

\*\* Figures interpolated from those given for 19 and 48 hours

Signs:  $<$  increasing = stationary  $>$  decreasing  $\wedge$  at a maximum

There are numerous data in the literature on the distribution of radioactive bismuth among organs but hardly anything about its accumulation in cells. The former distribution mainly depends on the medium in which the bismuth is introduced, e.g. whether in aqueous solution (6, 15, 16, 17, 19) in oil (6), bound to organic compounds such as carbonate lecithin (16, 17, 18) or protein (15), or absorbed on coal particles (3, 15, 22, 24). In connection with the present work, all results pertaining to the administration of bismuth other than in watery solution can therefore be left out of consideration. As far as the author is aware the first autoradiographic data on the distribution after injection of a bismuth salt dissolved in water was given by LACASSAGNE & FOUCAULD (6). These authors, 4 to 10 days after the injection into rabbits, found a very high accumulation in the renal cortex, a high concentration in the spleen, less in the liver, a scarcely perceptible amount in the bone marrow and practically none in lymph nodes, testes, thymus, adrenal and appendix. KAHN (5) reported an accumulation of  $^{210}\text{Bi}$  in tumours but not elsewhere. The findings of LACASSAGNE & FOUCAULD, although not presented on a quantitative basis, and determined at longer intervals after injection, more or less agree with those of the present investigation.

The only reports on the distribution after shorter time intervals are those by MATTHEWS (15) and PASSALACQUA (16, 17, 19), obtained by radiation

counting of  $^{210}\text{Bi}$  in entire organs and therefore not directly comparable with the results now given. As, however, the radiation countings are recorded as radioactivities per unit weight of kidney, liver, spleen, lung, and sometimes bone marrow, and as the track countings presented in this paper pertain to autoradiograms from uniformly thick sections of these same organs, some comparison of the relative radioactivities of these organs would seem possible. To this end, therefore, Table 3 was compiled. The results given by PASSALACQUA (16, 17, 19) for the 24 hour interval after administration of  $^{210}\text{Bi}$  nitrate in animals not bearing tumours are represented in relation to the radioactivity of the kidney (kidney = 100) in the table. The results by MATTHEWS for  $^{210}\text{Bi}$  citrate were also interpolated for 24 hours from her figures for 19 and 48 hours and likewise presented relative to kidney = 100. It is indicated in all cases whether the radioactivity seems to go up or down or to remain equal. The track countings from the present investigation, insofar as they were obtained from parts of organs (e.g. kidney tubuli, cortex, medulla), were converted to figures for the entire organs by due consideration of their composition as measured from serial sections, and the figures so obtained were again presented in relation to whole kidney = 100.

It is apparent from this table that there is a striking difference between the autoradiographic findings and all radiation counts (which among themselves are far from uniform). This must doubtless be ascribed to the fact that most of the bismuth that at the instant of fixation is still present in a soluble form will be washed out in the course of the histologic preparation for autoradiography. Most tracks in the autoradiograms will be derived from the  $^{210}\text{Bi}$  that is rendered insoluble either by the formation of larger aggregates or by binding to organic compounds. Although it has long been known that the isotope concentration and the method of injection may lead to varied degrees of aggregation (13), this does not seem to have been the case in any of the doses used in this investigation, because even in areas of the greatest track density no stars were evident. It must be concluded therefore that most of the autoradiographically detected  $^{210}\text{Bi}$  is bound to organic material, supposedly protein. The distribution of the tracks among all types of cells and tissues makes it seem likely that one day after injection the isotopes are still largely in a soluble form and freely pervading all tissues.

If it be assumed that the  $\text{Bi}$  ions on their course are somewhat randomly bound to organic matter, this would explain the presence of tracks over erythrocytes, connective tissue and bone, smooth muscle fibers of arteries and even over the histologically empty lumina of vessels and tubules. In such organs as accumulate the isotope(s), part of the amount incorporated by specific cells, such as the proximal tubuli cells of the kidney, may also have diffused out so that tracks are found over other cells of these organs as well.

The organs that specially accumulate the isotope for excretion are the kidney and, to a lesser extent, the liver, the bile of which was found to contain

much bismuth. If indeed both organs collect Bi mainly in the soluble form, this would explain why these two organs register a much lower relative radioactivity in the autoradiograms than in total organ counting (Table 3).

A random binding of freely pervading Bi ions would also explain why a ratio of only 5 to 7 was found for a tenfold increase in dose. The binding of the isotope to organic compounds would be less than proportional to its concentration, whereas a higher concentration would favour the loss by excretion.

It is certainly not claimed that all discrepancies may thus be explained. Due attention must be given to the fact that both the method of administration of the isotope (13) and its concentration (21) may influence the distribution in the body. As to the present investigation, it has already been stated that the first possibility does not seem likely, whereas the second is rendered less probable by the regularity observed in Tables 1 and 2. The main question left open is to what extent these results have been influenced by the unknown quantity of  $^{10}\text{Po}$  formed out of the  $^{210}\text{Bi}$ . If these isotopes had been accumulated by the various organs in a markedly different proportion, this would have resulted in a greater irregularity of the figures presented in the tables. Their very regularity makes it seem fair to assume that the behaviour of Bi and Po in the animals was roughly similar as long as no data to the contrary are recorded.

The distribution of polonium has been studied by LACASSAGNE and his co-workers (7, 8, 9, 10, 12, 14) in what have become classics of autoradiography. The investigations, however, were made at much longer intervals after injection (4 to 10 days) and then the accumulation in the renal tubuli, bile, and pulmonary dust cells (9) is much more marked, its accumulation in reticulum cells and macrophages even leading to extensive radiation damage (ref. 10, 14). As with bismuth, distribution depends on the medium in which the isotope is administered, after its introduction in an aqueous form the accumulation in the kidney was found to be especially marked (ref. 7). Indications on the distribution after 24 hours were reported only by GALLIMORE et coll. (2). Their figures for percentage of dose per gram wet weight were: kidney 2.8 (100), spleen 5.1 (183), liver 1.4 (50), or markedly different from those of the present investigation (Table 3). Their autoradiograms of tissues fixed after the same interval, however, show many striking likenesses with those now described.

Aside from a multitude of minor quantitative differences, the general picture for polonium, as for bismuth, is that 24 hours after injection the isotope is still far from being concentrated at its definitive locations. The element is reported to be eliminated from the organism with an effective half life of approx. 30 days (ref. 4) and it is therefore not surprising that after one day only the first indication of the future accumulation is evident.

The marked accumulation of the isotope(s) in the renal tubules observed in the present work has been found both for Bi and Po; moreover it seems

to be the rule for a great number of elements administered to the organism in a soluble form. This accumulation cannot therefore be considered to be specific for any isotopes.

The present observations do not give the clear cut distinction in the spleen between red pulp on the one hand and white pulp, vessels, and connective tissue on the other as reported by LACASSAGNE et coll (10) and GALLIMORE et coll (2) for Po. The slightly but systematically higher track density over the red pulp in the present work may however tentatively be considered to be a first indication of this distribution. Likewise, the inconspicuous accumulation in the macrophages may be explained as the beginning of the accumulation observed so definitely by LACASSAGNE after 6 days.

It appears therefore that such specific accumulation as has been found in the present work could almost equally as well be ascribed to the bismuth as to the polonium present in the injected material. There is no indication as yet for any cellular specificity for Bi in soluble form. It may be that such a specificity is overlapped by the Po present. In that case a repetition of the experiment with a very freshly prepared solution of  $^{210}\text{Bi}$  may produce clearer results. If however a specific accumulation of Bi does not develop until some days after the introduction of the isotope the accruing contamination by Po may well become prohibitive.

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### SUMMARY

Rats were injected intravenously with doses of  $^{210}\text{BiCl}_3$ , and counts and distribution studies of the tracks of autoradiograms of various tissues were performed. Track distribution in most cases conformed to the random distribution, the only exceptions being a high accumulation in the proximal tubules of the kidney and a slight accumulation in the macrophages of the spleen.

### ZUSAMMENFASSUNG

Ratten erhielten Einspritzungen von  $^{210}\text{BiCl}_3$ , worauf mit Hilfe von Autoradiogrammen von verschiedenen Geweben die Stärke und die Verteilung der Strahlungsemission gemessen wurde. Die Strahlung zeigte im allgemeinen eine gleichmässige Verteilung, eine Anreicherung zeigte sich jedoch in den proximalen Tubuli der Nieren und in den Makrophagen der Milz.

### RÉSUMÉ

Après avoir injecté à des rats par voie intraveineuse du  $^{210}\text{BiCl}_3$ , l'auteur a effectué des comptages et des études de distribution sur les autoradiographies de divers tissus. Cette distribution est dans la plupart des cas conforme au hasard, la seule exception étant une forte accumulation dans la partie proximale des tubes rénaux et une faible accumulation dans les macrophages de la rate.

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## COMPLICATIONS IN POST OPERATIVE IRRADIATION OF MAMMARY CARCINOMA

Observations in 585 patients treated at Radiumhemmet 1955—1960

by

FOLKE EDSMYR and RUNE WALSTAM

Different methods of irradiating parasternal lymphnode metastases have been investigated at Radiumhemmet. One of the methods particularly developed for this purpose was described by EDSMYR & WALSTAM in 1959 and physical conditions for certain techniques were compared in a later paper (STROM VINTERLOF & WALSTAM 1959). Postoperative irradiation of the parasternal region was performed in 585 patients from 1955 to 1960 on the basis of results from these investigations, from January 1958 until the end of 1960. 120 of these patients were treated with 9 or 12 MeV electron beams while in the other 465 patients a short distance cobalt 60 beam technique was used.

The treatments were started with relatively moderate doses since no experience had been gained either of early or of late reactions from the irradiated tissues. The plan if circumstances allowed was to increase the doses gradually so that as high a dose as possible could be given to the lymphnode areas without causing intolerable complications, functional disturbances or other radiation



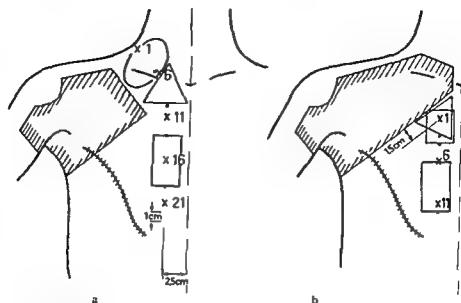


Fig 1 Scheme of irradiation with orthovoltage roentgen therapy and short distance cobalt 60 gamma beam therapy

- a) Overlapping field including the parasternal and supraclavicular regions  
 fields 1 to 5 SSD = 75 cm circular field diameter 6 cm  
 » 6 to 8 » = 75 cm triangular field side 5 cm  
 » 9 to 23 » = 6 cm field 3.5 x 6 cm  
 b) Overlapping field including only the parasternal region  
 Field 1 - triangular or partly covered field  
 Fields 2 to 14 - SSD = 6 cm Field 3.5 x 6 cm

reactions in surrounding organs (cf FLETCHER et coll 1962) The skin and lung reactions, subjective symptoms and local complications in patients thus irradiated will now be dealt with. The irradiation technique has successively undergone minor modifications suggested by the clinical observations. The effect of irradiation on any parasternal and supraclavicular lymphnode metastasis that may have been present cannot be assessed from this series for it is relatively heterogeneous and the observation time has in most cases been too short.

Preoperative roentgen irradiation (FSD 50 to 60 cm, HVL 0.8 to 1.0 mm Cu) was given in about two thirds of the patients and may be considered to have had some influence at least as far as skin reactions are concerned. The irradiation was generally administered in a week by giving 3 x 350 r to frontal and dorsal fields that included the mamma and the axillary and supraclavicular regions.

#### **Patients (465) treated by the short distance cobalt 60 technique**

**Irradiation technique** A special technique was developed at Radiumhemmet (WALSTAM 1958) for irradiation of elongated superficial areas with short distance cobalt 60 units. This comprises a great number (10 to 25) of over

lapping irradiation fields (SSD 6 to 10 cm) with some exceptions each field is irradiated once only, so that a homogeneous dose is obtained at the particular tissue depth. For further data on this technique the reader is referred to earlier papers (EDSMYR & WALSTAM 1959, STROM, VIKTERLOF & WALSTAM 1959).

Thirty-eight patients were treated by a preliminary technique during the period December 1st, 1955 to August 31st, 1956: a beam nozzle giving a field of 6 cm width at the skin at a source skin distance of 10 cm was used. All the other patients were irradiated according to the schemes outlined in Fig. 1. A specially designed beam nozzle giving a field of 3.5 cm width at the surface at 6 cm SSD, was then employed. Two irradiations in different parts of the treatment area were administered daily in many of the patients for whom a great number of irradiation fields were utilized. Only exceptionally was this procedure contraindicated, for instance by the patient's general condition. The total duration of a treatment series was therefore 10 to 20 days.

The dosage in short distance gamma beam therapy with radium or cobalt 60 because of measuring difficulties is generally expressed as the extrapolated skin dose. This dose which is arrived at by extrapolating the depth dose curve obtained in tissue equivalent material to the depth 0 is often 5 to 10 per cent higher than the true dose maximum found at a tissue depth of 1 to 2 mm. The surface doses now mentioned for instance the dose to each irradiation field (750 to 1 000 r) refer to the extrapolated skin dose. The total skin dose used in the applied overlapping field technique is generally about six times the dose prescribed for each field.

In the total group of 465 patients 213 were irradiated over both the supraclavicular and the parasternal areas whereas 252 patients received cobalt 60 irradiation over the parasternal region and orthovoltage roentgen therapy over the axillary and the supraclavicular regions.

*Skin reactions.* The skin reaction could be graded from the data of the records in 287 (62 %) of the patients irradiated by this technique according to the following schemes:

- I — moderate or slight reaction
- II — intense redness (no discharge)
- III — serous dermatitis (discharge)

The results from this grading are set out in Table 1.

The skin reaction should increase with increasing dosage to the fields. Such a tendency may be found in the preoperatively irradiated group but is hardly noticeable in the group of preoperatively non irradiated patients. It will be seen from the table that middle dosages 850 to 900 r comprise 216 patients or 75 % of the total number. The extreme groups are fairly small and cannot

**Table 1***Grade of skin reactions in patients treated by the short distance cobalt 60 technique*

Dose per field r	Number of patients	I reoperative irradiation in 189 (67) cases			No preoperative irradiation in 93 (31) cases		
		Grade I	Grade II	Grade III	Grade I	Grade II	Grade III
750	51	31	15	5	2	1	0
800	8	4	2	1	1	—	—
850	61	22	10	2	19	6	5
900	142	50	27	11	30	17	7
950	11	1	1	2	4	1	2
1 000	8	1	3	1	2	1	—
Total	287	109	58	22	58	26	14

**Table 2***Summary of results presented in table 1*

Dose per field r	Number of patients	I reoperative irradiation			No preoperative irradiation		
		Grade I	Grades II + III		Grade I	Grades II + III	
			Number	Percent		Number	Percent
750—850	126	57	35	38	22	12	35
900—1 000	161	52	45	46	36	28	44
Total	287	109	80		58	40	
Average				42			41

therefore be expected to give significant deviations. If the patients are divided into two groups only, the distribution shown in Table 2 is obtained.

The small difference in the frequency of heavy skin reaction (grades II + III) between the groups of patients who received preoperative roentgen therapy (42 %) and those who had no such treatment (41 %) is surprising. It should be borne in mind, however, that the preoperative irradiation was administered in short series about 3 weeks before the postoperative irradiation was started. Its cumulative effect is therefore difficult to assess.

The patients' records in a great number of instances (178) contained no data on skin reactions. It may therefore be assumed that in all these the skin reaction was of grade I, on this assumption the incidence of marked skin reactions (II or III) should decrease from 40 % to 25 % of the total number of patients.

The most marked skin reaction was generally observed in regions with a thin

skin layer, particularly over the bones in the sternoclavicular area, as was to be expected. Necrosis developed in the irradiated parasternal area after a dose of 900 and 1 000 r respectively per field in two patients. The necrosis appeared in one patient 18 months and in the other a year after the termination of irradiation. Both patients had received preoperative irradiation. The first mentioned patient was 35 years old and had severe anaemia before, during and after the treatment, which might have influenced the postoperative course and the healing. The other patient received a dose of 2 000 r to the first and the last treatment field, and it was in these regions that the maximum skin reaction and the necrosis occurred. Healing is now complete and without complications after plastic surgery.

Severe telangiectasis or superficial induration within the parasternal region occurred in the groups that had been given 850 r per field (5 patients) or higher doses. The numbers of such patients were 4 in the group of 900 r per field, one in the 950 r group and one in the 1 000 r group. Three of these eleven patients had not been irradiated preoperatively.

*Lung reactions.* Thirty seven of the 38 patients treated according to the preliminary technique at 10 cm SSD were examined roentgenographically for lung reactions immediately after the treatment and later. No changes considered referable to the radiation treatment were observed in 27. Among the other 10 patients four have still, after 5 years, residual radiation reactions, three have decreasing effects, and in three the changes have disappeared. No subjective symptoms have been reported apart from those occurring immediately after the termination of treatment.

Roentgenography of the lungs was performed in 164 of the other 427 patients, because of cough and increasing dyspnoea. A radiation reaction was evident in 40 (24 %) of these patients. The symptoms and signs disappeared after 2 to 3 months. No difference was noted in the lung changes between the groups given 750 to 850 r per field and those receiving 900 to 1 000 r per field.

*Subjective reactions.* The symptoms and signs were slight excepting the skin and lung reactions mentioned earlier. Induration was present, however, in the supraclavicular region in a small number of patients in each group; it caused a reduction of the range of movement of the corresponding arm and in some patients fairly intense brachial pain. No such complications were noted in the groups given 750 to 850 r per field but occurred in 2 patients in the group of 850 r per field, in 13 of the group with 900 r per field and in 2 patients in the group that received 1 000 r per field. The symptoms started about one year after the termination of the treatment.

Dysphagia and other disturbances due to radiation effects in the oesophagus such as are reported to follow irradiation by other methods (FLETCHER et coll 1962) have not occurred in any of the patients in the present series.

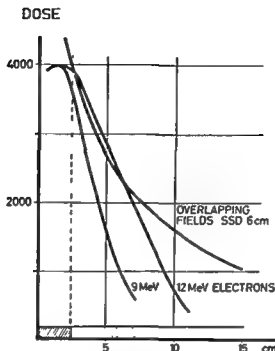


Fig 3 Approximate depth dose curves in the central part of the irradiated area (cf text)

the examination reveal evidence of radiation reactions. No difference in the lung changes between the 9 MeV group and the 12 MeV group were observed.

Among these 120 patients no important *subjective reactions* other than serous dermatitis in eleven (Table 3) and marked induration in the supraclavicular region in one patient were apparent.

The *local complications* and the changes in the *blood picture* that occurred in this group of patients were not sufficiently severe to be mentioned in the case records or to necessitate any alterations in treatment planned for the series.

### Discussion

The presence of metastases in the parasternal and supraclavicular lymphnode areas cannot as a rule be established in the individual case. The treatment of these regions is based mainly on a probability estimation, in which, for instance, the site of the primary tumour and the gross and microscopical appearance of the surgical axillary specimen are important factors. The irradiation is therefore planned to provide an adequate dose to those areas where metastases are particularly likely to occur, without causing serious unreasonable distress to the patient.

This investigation has shown that a dose of 850 r per field (extrapolated surface dose), when using short distance gamma beam technique or 4000 r per field in electron beam irradiation with the treatment times stated, does not produce any noteworthy side effects. Preoperative roentgen therapy with about 1000 r, 2 to 3 weeks before the postoperative radiation treatment does not seem to increase the skin reaction in any considerable degree.

The relative depth dose obtained with these treatment techniques in the middle parts of the treatment area and in the centre of the electron beam respectively is evident from Fig. 3. As pointed out earlier, a considerable spread of electrons is obtained in the lung cavities because of their lower density.

This material unfortunately permits no conclusions regarding the effects of the applied doses to any lymphnode metastases that may be present. The doses administered with these methods to the tissue volume concerned (cf. Fig. 3) seems, however, to be higher than the doses that because of the risk of skin and lung reactions can be given with orthovoltage roentgen therapy. Similar doses applied with a telegamma technique at larger source skin distances have been reported to cause serious pulmonary symptoms and dysphagia (FLETCHER 1962).

## SUMMARY

Two previously described methods for the irradiation of parasternal and supraclavicular lymphnode metastases have been used at Radiumhemmet: one based on the use of short distance gamma beam therapy, the other utilizing 9 or 12 MeV electrons from a betatron. A report is given of the irradiation conditions and the clinical observations in 585 patients treated with these methods during the period 1955-1960.

## ZUSAMMENFASSUNG

Zwei früher beschriebene Methoden zur Bestrahlung der parasternalen und supraclaviculären Lymphknotenmetastasen wurden am Radiumhemmet angewandt: eine Methode benutzte eine Gammastrahlung von kurzem Abstand, die andere Elektronen von 9 oder 12 MeV Energie. Der Bericht umfasst die Bestrahlungsfaktoren und die klinischen Einzelheiten von 585 Patienten, die mit den beiden Methoden in den Jahren 1955-1960 behandelt wurden.

## RÉSUMÉ

Deux méthodes précédemment décrites pour l'irradiation des métastases ganglionnaires lymphatiques parasternales et sus-claviculaires dans le cancer du sein ont été utilisées au Radiumhemmet: l'une basée sur l'utilisation d'une gammathérapie à courte distance l'autre utilisant les électrons de 9 ou de 12 MeV d'un béatron. Les auteurs présentent les conditions d'irradiation et les observations cliniques de 585 malades traités par ces méthodes de 1955 à 1960.

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(1958) 880

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## COMPUTER METHOD FOR TREATMENT PLANNING IN EXTERNAL RADIOTHERAPY

by

HANS HALLDÉN, INGER RAONHULT and BENGT ROOS

Digital computers have proved to be very suitable for the calculation of dose distributions in radiotherapy with fixed or moving fields. In the automatic dose calculation methods described by THIEY (1955-1958) and STERLING, PERRY & BAHR (1961) polar co-ordinate systems were used and the methods were restricted to beams intersecting in one point and to symmetrical beams. SILER & LAUGHLIN (1962) schematically described a more generally applicable method. Cartesian systems are used in the computer method described below. It is not limited to symmetrical fields but is applicable to beams of any shape. The method has been tried for different combinations of roentgen and cobalt 60 beams and has been in practical use for about a year. It is now used mainly for the planning of cobalt treatments.

*Isodose diagrams and codes* The isodose curves of the cobalt beams are measured in a water phantom with an ion chamber connected to an automatic isodose recorder (LARSSON, LIDÉN & STARFELT 1963). Source surface distances (SSD) of 60 and 80 cm are used and distributions with normal and oblique incidence, as well as with a number of wedge filters, are measured.

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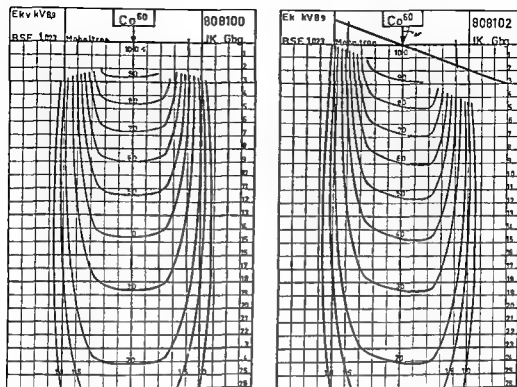


Fig 1 Isodose diagrams for 80 cm SSD  $Co$  field size  $8 \times 10$  cm, angles of incidence 0 and 20

The following code is used to identify the parameters

$$S a a b b u$$

where  $S$  = SSD in decimeters  $a a$  = field width in centimeters  $b b$  = field length in centimeters  $u$  = the angle between the central beam and the normal at the entrance point in deca degrees (For wedge filter diagrams we use  $u = 5$ )

Isodose curves for SSD = 80 cm field size  $8 \times 10$  cm<sup>2</sup> and angles of 0 and 20 between the central beam and the normal are shown in Fig 1 The codes 808100 and 808102 are shown in the upper right corners of the diagrams

Before the isodose charts can be used for computing, they must be transferred to digital form The depth doses in per cent are read off at a number of points in a Cartesian system The values are obtained from the measured curves by interpolation, and are expressed in per cent (excluding decimals) The previously shown isodose diagrams transformed into digital lattices are shown in Fig 2

These field matrices are punched on paper tape, which is read into the

808100

Symmetry **YES**

Max with 13 units

Max 1 gth 25 w t

[illegible]

808102

Symptom 1 NO

Maximum width 13 units

March 26, 1961

									100	99	97	80	45	15	3
								99	98	95	93	80	45	15	3
			75	90	93			93	92	90	75	45	15	3	
3	14	42	73	86	88			88	87	84	72	45	17	4	
4	15	42	70	83	83			83	81	79	69	43	18	4	
4	16	42	67	78	79			78	76	74	64	40	18	5	
5	18	41	63	74	74			73	72	69	60	39	19	5	
5	19	40	60	69	69			68	67	64	57	37	19	7	
6	20	39	57	64	64			63	62	60	53	35	19	7	
6	20	37	53	60	60			59	58	56	50	36	19	7	
7	20	35	49	56	56			55	54	53	47	33	18	8	
8	19	34	46	52	52			52	51	49	44	31	18	8	
8	18	32	43	48	48			48	47	45	40	30	18	8	
8	18	30	41	45	46			44	43	42	38	29	17	8	
8	17	29	38	42	42			42	41	39	35	27	16	8	
8	16	28	36	39	39			39	38	37	33	26	16	8	
8	16	26	33	36	37			36	35	34	31	24	15	8	
8	15	24	31	34	34			33	33	32	29	23	15	8	
7	15	22	29	31	31			31	30	29	27	22	15	7	
7	14	21	27	29	29			29	28	27	25	20	14	7	
7	13	20	25	27	27			27	27	26	24	19	13	7	
6	13	18	23	25	25			25	25	24	22	18	13	7	
6	12	17	21	23	23			23	23	22	21	17	12	7	
6	12	16	20	22	22			22	22	20	19	16	12	6	
6	11	15	19	20	20			20	19	19	18	15	11	6	
6	10	14	17	19	19			18	18	18	17	14	11	6	

Fig. 2. Field matrix as obtained from the nodose diagrams in fig. 1.

computer where controls are made then the information is stored in a format more suitable for the dose planning program

A more rapid and accurate method of producing field matrices would be to let the ion chamber scan the radiation field and directly to record the doses at the different points of the lattice.

**Coordinates and angles** The contour of the body cross section is drawn on transparent paper. The co ordinate axes and a contour with two treatment fields are shown in Fig 3. The  $x$  and  $y$  co ordinates of the entrance points of the beams are read off. The beam direction angle  $\epsilon$  is found when the positive  $y$  axis is turned clockwise until it coincides with the direction of the central beam. The

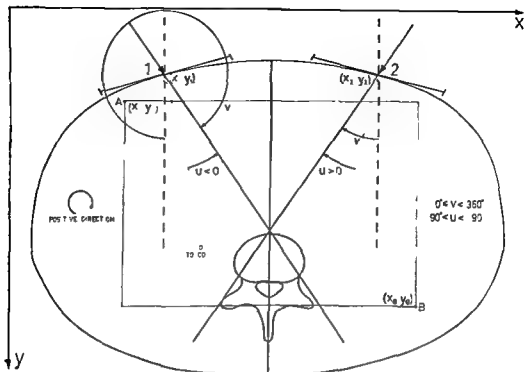


Fig 3 Schematic diagram showing co-ordinates and angles

Table 1

Dose planning Nr 33/621113

Field	Sym pos neg	x	y	k	t
808102	neg	74	02	100	330
808100	sym	262	28	100	50
808102	neg	221	197	100	140
808102	pos	08	181	100	240
A <span style="border: 1px solid black; display: inline-block; width: 100px; height: 20px; vertical-align: middle;"></span> B			x	y	
			0	0	
			29	21	

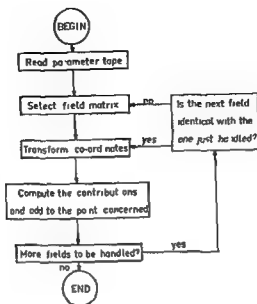


Fig. 4. Block diagram showing the computer program.

boundaries for  $v$  are  $0 \leq v < 360^\circ$ . The angle of incidence  $u$  is defined as the angle between the central beam and the normal to the contour at the entrance point and varies between the limits  $-90^\circ$  and  $+90^\circ$ . It is defined as positive if the normal mentioned can be brought to coincide with the central beam by a positive (clockwise) turn. In Fig. 3  $u$  is negative for field 1 and positive for field 2.

The area within which the computer has to add the contributions from the fields is chosen as a rectangle that well covers the tumour region as well as other regions having importance for the treatment. The maximum size of this rectangle is 48 cm along the  $x$  axis and 32 cm along the  $y$  axis. The co-ordinates for the two corners  $A$  and  $B$  defining the rectangle and all the radiation parameters mentioned above are recorded on an order form (Table 1).

### The computer program and examples

The program is described by the block diagram (Fig. 4) so we will just make a few remarks.

The data on the order form is transferred to paper tape and the result is given on paper tape.

The computer work follows a program with about 1 500 instructions.

The wanted contribution from one field to a point  $(x, y)$  in the area is determined as follows.

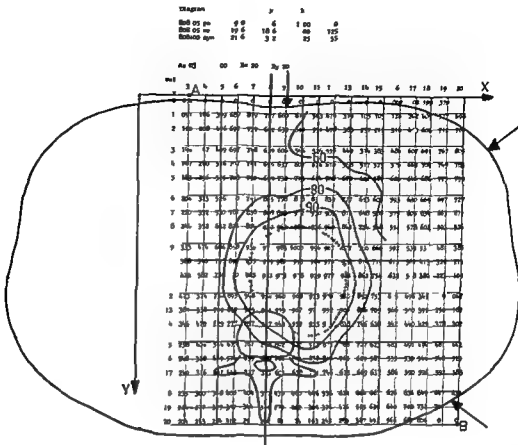


Fig 5 The figure shows the isodose lines being drawn on the cross-sectional diagram which is super imposed on the result form. The completed diagram is shown in fig 7

Let  $F(x, y)$  be the dose at the point  $(x, y)$  then if  $F(x, y) = Ax + By + Cxy + D$  we have to find the four constants  $A, B, C$  and  $D$ . First we transform the co ordinates of the point to the co ordinate system of the field, and there it usually becomes surrounded by four points, which we give the co ordinates  $(0, 0)$ ,  $(1, 0)$ ,  $(0, 1)$  and  $(1, 1)$  with the doses  $F(0, 0)$ ,  $F(1, 0)$ ,  $F(0, 1)$ , and  $F(1, 1)$ .

$$\begin{aligned} \text{Then } F(0, 0) &= D \\ F(1, 0) &= A + D \\ F(0, 1) &= B + D \\ F(1, 1) &= A + B + C + D \end{aligned}$$

$$\begin{aligned} \text{and } D &= F(0, 0) \\ A &= F(1, 0) - F(0, 0) \\ B &= F(0, 1) - F(0, 0) \\ C &= F(1, 1) - F(1, 0) - F(0, 1) + F(0, 0) \end{aligned}$$

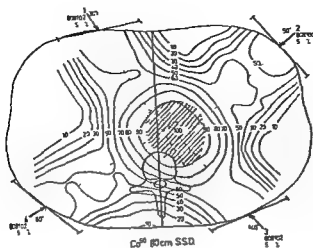


Fig 6 Distribution resulting from four fields

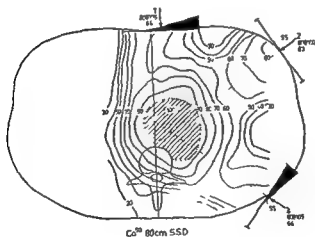


Fig 7 Dose distributon obtained from two wedge fields and one normal incidence field

and these constants multiplied with the decimal fractions of the transformed co-ordinates according to the formula give us the dose contribution from this field to this special point

The result paper tape is written out on a flexowriter. Over the result film we put a film with 1 cm squares and over this the transparent paper with the body cross section. On this paper the isodose curves are easily drawn (Fig 5). This last moment can be omitted if the computer is connected to a plotter.

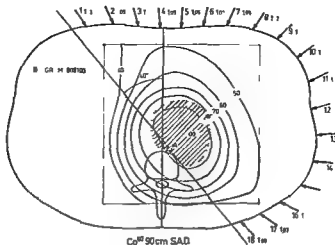


Fig 8 Dose distribution obtained from 18 fixed fields simulating moving field irradiation with 180° oscillation angle

The usefulness of the method is illustrated by three examples which show some different proposals for treating a tumour

*Example 1* is calculated with the parameters of the Table, and the percental dose distribution obtained, is shown in Fig 6

*Example 2* illustrates how with three fields we get a somewhat different distribution (Fig 7) (Fig 5 shows how the isodose curves are drawn on the transparent paper)

*Example 3* is an arc therapy calculation with an oscillation angle of 180°. The positions of the oscillation axis and of the fields are marked in Fig 8. The computing is done with 18 fixed fields with 10° angular intervals, size 8 × 10 cm<sup>2</sup>, source axis distance (SAD) = 90 cm. Here we have to consider that the SSD is a variable. The variation in SSD has a negligible influence on the isodose distribution and on the percental depth dose, but the dose rate at the different entrance points has a considerable variation, and hence the contribution from each field has to be multiplied by a factor. This factor is automatically computed by means of the inverse square law.

*Checking, errors, and corrections* The manual calculation of the dose at a few essential points is a precaution that always should be taken. On a comparison of these check values with the computer result it is found that the computed values are often a few per cents below those calculated by hand. The greatest errors appear at the field borders and are due to the fact that the computer fills

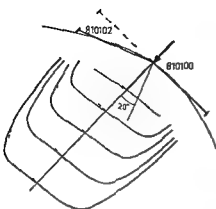
Co<sup>60</sup> 80cm SSD

Fig 9 Mixed isodose diagram

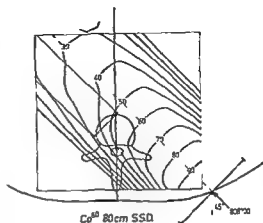


Fig 10 Distribution obtained when the correction factor 0.90 is applied to points in the rectangle behind the vertebra

the empty columns of the field matrix with zeros, so that the interpolation formula gives an underestimated dose at a point surrounded by one or more field points with the value zero. These marginal errors which generally are of secondary importance will be smaller if we increase the width of the field matrices but as this would increase the work to read off the diagrams we have to balance the errors to the extra work. Near the central axis the errors usually lie between 0 and 2% which we consider a sufficient accuracy.

When a field is applied obliquely to the body surface we use the proper measured diagram. There is, however, sometimes a need for diagrams which on one side of the central beam are close to normal incidence and on the other side to oblique incidence (Fig 9). Mixed diagrams of this kind are easily produced by the computer.

When irradiating tumours in the thorax region we can compensate for the increased transmission in the lung tissue either by moving the entrance points of the fields closer to the tumour or by introducing tissue factors.

For the decreased transmission in bone tissue we can compensate in a similar manner. In those cases where only a part of the beam is penetrating bone we can use the tissue factor within a limited area of the field matrix. The isodoses when the field points within the rectangle are multiplied by the factor 0.90 are shown in Fig 10.

*Series of standard dose diagrams* The computer method described above is well suited for precalculation of standard multiple and moving field dose distributions (DAHL & VIKTERLOF 1960; PFALZNER 1962). Calculations on a series of fixed field distributions of circular cross sections are carried on.



## SUMMARY

A method of automatic computation of dose distributions in multifield and moving field therapy is described. The isodose diagrams have been transferred to numerical lattices in a Cartesian system and punched on paper tape. The treatment area has been drawn in another Cartesian system in which the dose contributions from the different fields are added at a number of points. The calculation was carried out on a digital computer. The method is illustrated by examples and corrections for different types of tissue are discussed.

## ZUSAMMENFASSUNG

Eine Methode zur automatischen Berechnung der Dosisverteilung bei Kreuzfeuer oder Bewegungsbestrahlung wird angegeben. Die Isodosenkurven wurden in numerische Matrizen eines kartesischen Koordinatensystems überführt und auf Papierstreifen gestanzt. Das Bestrahlungsgebiet wurde in ein anderes kartesisches System eingezeichnet, in dem die Dosisbeiträge der verschiedenen Felder in einer Anzahl Punkte addiert wurden. Alle Berechnungen wurden mit Hilfe eines digitalen Computers ausgeführt. Die Methode wird an Beispielen illustriert und Korrekturen für verschiedene Gewebsarten werden besprochen.

## RÉSUMÉ

Description d'une méthode de calcul automatique de la distribution de dose dans le traitement par champs multiples et par cyclothérapie. Les courbes isodoses sont reproduites en coordonnées cartésiennes puis transcrites sur bande perforée. La région à traiter est représentée sur un graphique où les distributions de dose provenant des différents champs sont additionnées en un certain nombre de points. Le calcul est effectué par une calculatrice digitale. Les auteurs donnent des exemples de cette méthode et étudient les facteurs de correction pour les différents tissus.

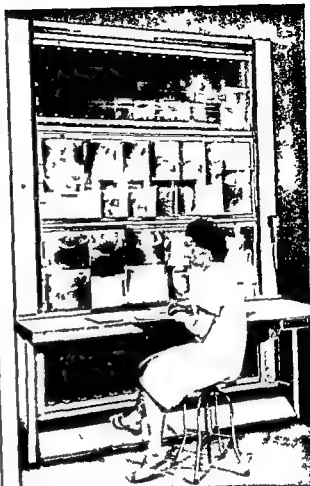
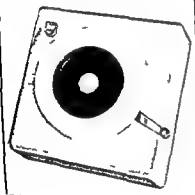
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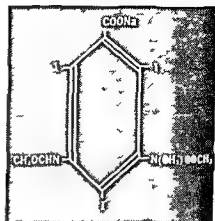
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## GIANT HEMANGIOMA AND THROMBOCYTOPENIA IN A NEWBORN INFANT TREATED BY IRRADIATION THERAPY

### Case report

by

U FURUHJELM, P MAELA and A VOUTILAINEN

The simultaneous occurrence of hemangiomas and thrombocytopenic purpura is unusual. The first report of a case of this now generally accepted clinical syndrome was published by KASABACH & MERRITT in 1940 and more than 40 cases have since then been quoted in the literature. HILL & LONGINO (1962) described two cases of their own and reviewed earlier case reports.

The size of the tumour and the severe bleeding tendency in these patients frequently pose considerable therapeutical problems. The present case concerns a newborn baby with a rapidly growing hemangioma and severe thrombocytopenia in which good clinical improvement was obtained by roentgen irradiation therapy.

### Case report

A boy born by spontaneous delivery after a full term uncomplicated pregnancy, weight at birth 4 450 g, general condition good and skin colour normal. A large tumour which appeared to be a hemangioma was evident in the left thigh, no petechiae or other signs of bleeding were

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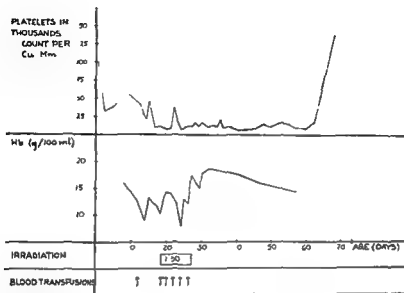


Fig 1 Hemoglobin concentration and platelet count while in hospital. The days on which transfusion and roentgen therapy were given are indicated.

apparent. When the child was two days old the hemoglobin value was 16.7 g/100 ml and the thrombocyte count 99 000/mm<sup>3</sup>. On the fourth day the thrombocyte count had dropped to 33 000/mm<sup>3</sup> and the child was transferred to the Childrens Clinic.

On admission the child's condition was still good and no signs of bleeding were evident. The liver extended 3 cm below the costal margin and the spleen was not palpable. An elevated hemangiomatous mass, purple in colour, firm and immovable and 1.5 cm in size, was present over the right thigh, almost the whole of which was involved except for a small area posteriorly. The adjacent skin was not sharply demarcated from the mass. The leg appeared to be otherwise normal. The hemoglobin concentration was 15.5 g/100 ml and the white cell count 14 300/mm<sup>3</sup>; the thrombocyte count was 59 000/mm<sup>3</sup>. The variations in hemoglobin concentration and platelet counts are depicted in Fig 1. The prothrombin and bleeding times were normal. Tibial bone marrow aspiration disclosed a cellular marrow with slight myeloid hyperplasia and normal erythropoiesis; megakaryocytes were present and seemed to be increased in number though they were normal in form and possessed a granular cytoplasm. Biopsy suggested a capillary hemangioma with considerable endothelial proliferation.

Röntgen examination revealed only soft tissue swelling of the thigh; the bone appeared to be intact. The tumour increased progressively in size during the following two weeks to form a circular mass that extended distally below the knee and proximally to the gluteal region (Fig 2). There was marked edema of the leg.

From the age of two weeks the child bled continuously from numerous small ulcerations on the surface of the tumour; at the same time he gained as much as 100 g a day in weight though this may be attributed in part to bleeding into the mass. The blood loss was considerable and sufficient blood volume was maintained by frequent transfusions of fresh blood, 800 ml in all were given (Fig 1).

Irradiation therapy was started when the child was 18 days old. The tumour was cross fired through two fields each measuring 8 × 10 cm, factors 180 kV, filter 5 mm Cu, FOD 40 cm and HVL 1.1 mm Cu. A total of 1 150 r to each field was given on consecutive days in single



Fig 2 Appearances of tumour prior to treatment



Fig 3 The thigh at the control examination

doses of 300 r with one of 250 r. A lead rubber sheet 3 mm thick was used to protect the gonads and epiphyseal lines. The secondary radiation caused by each single treatment (300 r) was measured as being 2.3% to the gonads and 2.0% to the nearest epiphyseal line.

The tumour felt much harder after a few days and there were signs of inflammation which included local elevation of temperature and maceration of the skin. The growth of the tumour was clearly inhibited and in spite of persistently low platelet counts the bleeding subsided towards the end of the treatment period. Clear improvement in the baby's general condition which had been rather poor during the period of severe bleeding was apparent at this stage. On the other hand there was no marked change in the size of the tumour and it was not until 38 days after the treatment was completed that the platelet count rose dramatically and then remained normal (Fig 1). The skin lesions also gradually healed and the child was discharged after 67 days in hospital.

At control examination 3 months later when the baby was 5 months old his general condition seemed to be satisfactory. The tumour had almost disappeared leaving a fibrotic scar formation 5 × 10 cm in size and firm to the touch. There was no difference in the circumference of the thighs (Fig 3). The peripheral blood picture was normal as was the bleeding time. The thrombocyte count was 260 000/mm<sup>3</sup>. The growth of the femora appeared roentgenographically to have been equal.

### Discussion

Thrombocytopenia and a tendency to bleeding in connection with a hemangioma is rare immediately after birth. Hemorrhage in this period constituted a problem in only 5 of reported cases (HILL & LONGIRO 1962). The remaining cases reported were mostly in infants and children with a few in the older age

groups. The thrombocytopenia usually appears during a period of rapid growth of the tumour, though cases with multiple small hemangiomas have also been described (GILON *et coll.* 1959, FISCHLER 1960). Diagnostic difficulties may arise when the hemangioma is situated subcutaneously or internally, e.g. in the intestine (JAMES & TUTTLE 1961, HILL & LONGINO 1962, BACKMAN & PARKKULAINEN 1958). Because of the tendency to severe bleeding, biopsy has been performed only in a limited number of cases and has revealed either a simple benign hemangioma, a capillary hemangioma or a hemangioendothelioma. Reports of bone marrow studies have not, however, recorded significant abnormalities except for immature megakaryocytes and a decreased or an increased number of these cells.

Several theories have been put forward to explain the process by which the thrombocytopenia is produced (SILVER *et coll.* 1948, SOUTHARD *et coll.* 1951, GOOD *et coll.* 1955, GILON *et coll.* 1959, BLIX & AAS 1961).

Various therapeutic measures, including supportive treatment, have been used in this syndrome. Steroids have occasionally been administered but without obvious beneficial effect on the thrombocytopenia (HILL & LONGINO 1962). They may, however, have prevented bleeding by raising the capillary resistance. Splenectomy has been performed in 8 cases with resultant improvement in the thrombocytopenia in one case (MEEKS *et coll.* 1955). Infusions of platelet concentrations restore the bleeding time to normal only for a very limited period but are of the greatest value before and during operative procedures.

The choice of treatment appears to lie between radical removal of the tumour and irradiation therapy. If the hemangioma is successfully excised there is a prompt rise in the platelet counts (INGLEFIELD *et coll.* 1961, HILL & LONGINO 1962). Operation is, however, ruled out in many cases because of technical difficulties or because of the great risk of excessive bleeding. Roentgen treatment results in cessation of the growth of the tumour and in its gradual shrinkage. The rise of the platelet count is slower than after surgery and occurs from one to several weeks after the treatment (SOUTHARD *et coll.* 1951, JAMES & TUTTLE 1961, SUTHERLAND & CLARK 1962). The period was about 5 weeks in the present case, on the other hand the bleeding from the tumour ceased much earlier when the treatment was completed, apparently as a result of the irradiation.

The irradiation dose was the usual one for hemangiomas and other benign tumours. The depth of the tumour was estimated to be approximately 3 cm, and a HVL of 1.1 mm Cu was used. The expected results were achieved: the growth of the tumour was checked, the thrombocyte count became normal and there were no signs of epiphyseal damage evident at the follow-up examination.

Disapproval of irradiation therapy is based upon the fear that secondary radiation may damage the gonads and epiphyseal lines. The total gonad dose in the present case was 18 r and 104 mr, and the dose to the femoral epiphyses

15 r and 320 mr respectively. The therapy would appear to have caused no somatic damage but it is of course too early to evaluate possible genetic disturbances.

The writers believe that irradiation is indicated for cases with massive hemorrhages where radical treatment is impossible. A combination of irradiation and surgery might be advantageous, the acute stage could be controlled by radiation therapy and the tumour excised later (HILL & LONGINO 1962).

## SUMMARY

A case of a newborn boy with a rapidly growing giant hemangioma and thrombocytopenia treated with roentgen irradiation is reported. The treatment resulted in a decrease in the size of the tumour and a rise in the platelet count. Some of the therapeutical aspects are briefly discussed.

## ZUSAMMENFASSUNG

Ein Fall von einem neugeborenen Jungen mit einem rasch wachsenden Riesenhaemangiom und mit einer Thrombocytopenie behandelt mit Röntgenstrahlen wird beschrieben. Die Behandlung führte zu einer Verkleinerung des Tumors und einer Besserung in den Thrombocyten. Einige Punkte der Therapie werden erörtert.

## RÉSUMÉ

Les auteurs présentent le cas d'un garçon nouveau né atteint d'un hémangiome géant croissant rapidement et de thrombocytopenie qui fut traité par roentgentherapie. Le traitement amena une diminution du volume de la tumeur et une augmentation du nombre des plaquettes. Les auteurs discutent brièvement certains problèmes concernant le traitement.

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## LONG TERM STUDIES IN DOGS RECEIVING SINGLE MASSIVE INJECTIONS OF RADIOACTIVE IRON DURING GROWTH

by

P F HAIN and E L CAROTHERS

Concern as to the long term effect of internal exposure to radioactive isotopes is not new. Interest originally centered not only on the pseudo-medical use of water containing radon many years ago but also on those individuals who were exposed by their own carelessness, ignorance or otherwise to radium in the course of dial painting during World War I. Such individuals have been studied extensively by many workers. The increase in potential exposure to long lived and therefore possibly carcinogenic and genetically important artificially produced radioactive isotopes and fission products has resulted in the extensive re investigation of the effects of exposures to such agents in laboratory animals and also in humans. A great amount of such work has for many years been carried on at Argonne National Laboratory, and its predecessor the Metallurgical Laboratory of the University of Chicago in connection with the study of strontium barium cesium yttrium and plutonium in experimental animals. Similarly studies on the concentration and long term effect of plutonium polonium and radium have been conducted at the University of California at

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Berkeley, and at the University of Rochester. More recently the effects of relatively long lived  $^{14}\text{C}$ , tritium and uranium isotopes have been studied at various laboratories. Strontium 90 is of course one of the fission products which is currently being widely investigated as to its carcinogenic potentialities at various levels of introduction by different routes.

We have always looked upon any nuclide with a half life of ten days or more, especially one which has a tendency to concentrate in specific tissues, with a degree of suspicion as concerns carcinogenicity when introduced in quantities which are currently thought to be dangerous. Our concepts of maximal permissible doses are necessarily undergoing re evaluation with increasing experience but in general one might say that American usage of isotopes has been on the conservative side.

In 1941 we first described the use of the  $^{59}\text{Fe}$  isotope for tagging the hemoglobin of red blood cells in donor dogs for the purpose of determining the circulating mass of erythrocytes of recipients (6) (7). The chief advantage of this method over that used by HAHN and HEVESY, and subsequently by NYLIN using  $^{32}\text{P}$  rested in the fact that once established in the hemoglobin molecule the iron was firmly bound and remained within the red cell throughout its life span. In using iron as a tag there was no constant exchange in the body of the label with that of other compounds containing iron (4). The chief disadvantage in the use of the  $^{59}\text{Fe}$  isotope by the method described lay in the technical problem of building up donors and also in the complicated methods required for measurement of the iron radioactivity in 1941.

World War II brought to the front two major problems in which the iron tagged red cells proved to be of considerable value, namely in the investigation of shock and in the study of blood preservation. After considerable amount of experience under battle conditions, it was finally recognized by the Armed Forces that where considerable blood loss had occurred the infusion of whole blood rather than plasma was required to combat shock. Therefore several major programs were established to determine what materials would constitute the best preservatives for whole blood and/or red cells. Studies of this sort were set up under the leadership of various investigators and these individuals also used the donor tagging technique in their human studies. Our own efforts (8) (9) and that of many others were confined largely to the study of the red cell and total blood volumes in malaria, shock, polycythemia and other conditions of interest.

In present day tracer studies for diagnostic purposes every effort is made to reduce the amount of total radioactivity introduced into a relatively normal individual. With improved instrumentation the use of smaller and smaller quantities of isotopes is feasible. However, during World War II the instrumentation methods were far from ideal necessitating the employment of larger amounts of radioactivity. This was particularly true in the case of volunteer donors who were employed for the studies mentioned above.

It has been shown following the administration of iron to growing animals that nearly complete utilization of this material is accomplished in formation of hemoglobin in the peripheral circulation (5) and that once established the iron is re utilized repeatedly in red cell hemoglobin construction (1) The  $^{55}\text{Fe}$  activity is dissipated in six half lives which one would expect to span two life cycles of the red cells Therefore these isotopes with their long half lives ( $^{55}\text{Fe} = 47$  days and  $^{59}\text{Fe} = 2.9$  years) by their nature carry with them a low level of constant irradiation over long periods of time Fortunately the spectra of these isotopes are such that little radiation beyond the vascular system is anticipated With the  $^{55}\text{Fe}$  isotope the beta component is quite weak and in the case of the  $^{59}\text{Fe}$  the K capture electron results in the emission of a very soft roentgen beam Nevertheless it seemed advisable to determine whether or not any recognizable deleterious effects might be noted in long term experiments in animals in which the circulating titre of radioactivity was increased manifold over that used in the past

It was thus decided to study whether in the dog  $^{55}\text{Fe}$  in quantities of many hundred times those employed in the war time studies could be tolerated without embarrassment of the hematopoietic system or ultimate development of neoplastic conditions For this reason in October 1950 and again in June 1952, a litter of hounds, in each year, was injected with the maximal quantities of radioactivity available at those times in the form of radioactive iron

### Methods

$^{55}\text{Fe}$  is usually made by either a d p reaction in the cyclotron or by an n y reaction in the pile Its production efficiency is low primarily due to the small natural abundance of the parent  $^{54}\text{Fe}$  isotope this being only about 0.25 per cent normally Specific activities necessary for the use of large total radioactivities would thus not be normally attainable within the toxic limits of the amount of iron which would have to be administered Therefore for our purpose  $^{55}\text{Fe}$  was enriched by electromagnetic separation procedures at Oak Ridge (We are indebted to Dr P. C. Aebersold who made the arrangements for electromagnetic concentration and subsequent special bombardment of the iron used in these studies) The resultant 80 per cent abundant isotope was then subjected for several months to the thermal neutron flux of high intensity at Hanford Washington The resultant material contained approximately 1 millicurie  $^{55}\text{Fe}$  activity per milligram of iron Thus in 1950 and 1952 the total and specific activities were very considerably greater than those previously produced The material was prepared in colloidal form and administered by vein to the dogs in order to ensure maximum utilization

The dogs in the first experiment in 1950 were litter mates and were marked 50-1, 50-2, 50-3 and 50-5 They were nearly pure bred blue tick hounds They were approximately two months of age when acquired with their mother

**Table**  
*Annual summary of hematologic examinations and growth*

Dog	Date	RBC	Hct	WBC	Segs	Lymph	Staffs	Juv	Eos	Mono	Wgt Lbs
50—1 (treated) litter I ♀	10- 5-50	7 64	44.5	16 000	III	13	21	3	2	10	29.0
	10- 5-50	1 mC of <sup>59</sup> Fe injected I V									
	9-22-51	5 12	49.0	13 850	42	38	6		III	2	33.5
	9-25-52	7 67	54.0	12 100	42	35	13		8	2	38.0
	9-23-53	4 74	48.0	13 450	57	34	6		1	2	41.1
	9-29-54	7 47	49.0	13 150	65	32			3		45.0
	10- 1-55	6 42	52.0	8 950	69	14	15			2	46.2
	9-29-56	5 41	51.0	12 000	69	25	5		1		49.0
	11-29-56	Sacrificed and autopsied									
											48.5
50—5 (control) litter I ♂	10- 5-50	8 26	47.0	11 600	46	21	III	2	1	12	29.0
	9-22-51	5 41	50.0	10 425	41	30	11		16	2	37.1
	9-23-52	7 95	52.0	13 450	58	20	11		8	3	39.7
	9-23-53	7 72	49.0	14 875	69	22	1		8		8.8
	9-29-54	8 09	55.0	9 550	67	29			4		39.5
	10- 1-55	7 23	58.0	6 500	60	19	16		3	2	39.9
	9-29-56	6 10	56.0	9 025	53	33	11		1	2	41.0
	11-29-56	Sacrificed and autopsied									
											41.0
50—218 (con- trol) litter II ♂	6-27-52	5 09	39.0	18 050	68	21	4		5	2	28.0
	6-24-53	4 38	50.0	13 875	71	25	2		2		35.5
	6-30-54	6 95	51.0	9 325	77	23					35.0
	6-28-55	7 92	59.0	6 975	46	21	11		16	6	34.0
	6-27-56	7 51	53.0	16 725	69	20	5			6	33.7
	9-29-56	6 12	56.0	6 725	66	27	2		3	2	34.0
	11-29-56	Sacrificed and autopsied									
											34.8
50—221 (trea- ted) litter II ♂	6-27-52	6.24	40.0	20 000	III	23	4		5	7	16.6
	6-28-52	3.3 mC of <sup>59</sup> Fe injected I V									
	6-24-53	7.57	58.0	14 225	67	29	3		1		38.5
	6-30-54	5 70	48.0	12 550	76	24					38.4
	6-28-55	7 23	55.0	12 625	79	6	10		3	2	41.3
	6-27-56	6 90	56.0	11 700	71	13	3		4	9	45.0
	9-29-56	6 17	52.0	10 725	51	29	9		8	3	43.2
	11-29-56	Sacrificed and autopsied									
											44.2

(50—4) on 23rd of June 1950. At that time they were vaccinated against distemper and dewormed. The first three dogs of this litter were injected at six months of age with 1 mC each of <sup>59</sup>Fe during an active growing period without previous phlebotomy. A control litter mate, 50—5, maintained as the others on a commercial diet of 'purina dog chow', was not injected with radioactive material. Before injection erythrocyte count, hematocrit and leucocyte count, including differential counts, were found to be within normal limits.

GENEALOGY OF INTERBRED DOGS

Chart I — 50 1

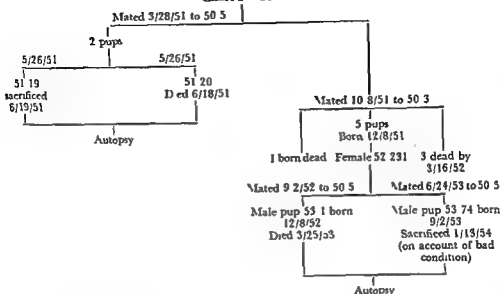


Chart II — 50-2

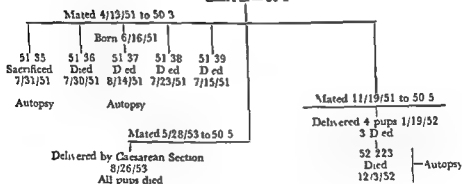
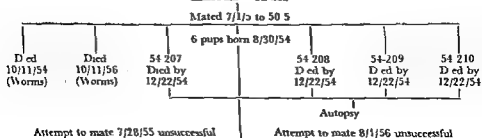


Chart III — 52 222



All the puppies had shown normal development and had gained weight during a period of four months between acquisition and injection.

Hematologic studies were carried out at monthly intervals for the next six years by five individual student fellows working approximately one year each (The hematologic examinations were performed by Marvin Jackson, Frank Staggers, James Utey, William Andrews and Douglas Foster.) Data are summarized in the Table. These consisted of hematocrit values, erythrocyte and leucocyte counts, differential counts and sedimentation rates. The weights, and signs of clinical well being of these animals, were also recorded regularly for six years. On July 28, 1953, a test study of thick dehemoglobinized smears was negative for microfilaria on all dogs of both litters. At the end of five years, bone marrow (rib) biopsies were obtained, and at the end of the sixth year these animals were sacrificed in November 1956 for gross and histologic analyses by the use of intravenous pentobarbital sodium in excess. The dogs 50—2 and 50—3 had for various reasons died before this date.

After having become adults (approximately one year of age) these animals were interbred whenever possible. Dog 50—1, which had received  $^{59}\text{Fe}$ , was mated a year after injection to a male litter mate 50—3, also injected with iron, and as a result five pups were born on December 8, 1951. Of these, one was born dead and three of the others were dead within three months time. However, one female, 52—231, survived throughout the ensuing five year period. She was sacrificed along with all the other living animals in November 1956. In the meantime she was mated on two occasions with the control litter mate 50—5 of the original group (see genealogy chart I) and as a result of the first pregnancy had one male pup which lived three and a half months, dying, as far as could be determined, of pneumonia. The second pregnancy of 52—231 also resulted in the delivery of a single male pup born on September 2nd, 1953 and this animal was sacrificed four months after birth in poor condition, and autopsy again revealed pneumonia as the cause of death. It is to be noted that in none of the second and third generation inbred animals were there any notable changes either grossly or histologically. No visceral changes were encountered or hematopoietic alterations suggestive of any deleterious effect due to the burden of radioisotope in the predecessors. It is apparent that our animal house was unsuitable for breeding and maintenance of puppies. Therefore, there was a limited number of surviving of first and second generation animals to be studied.

The dogs 52—218, 52—219, 52—220, 52—221, 52—222 (control 52—218) in the second experiment were also litter mate hounds of about half the weight of the earlier group, and were injected with  $^{59}\text{Fe}$  on June 28, 1952, as follows: 52—218 (control none), 52—219 received 0.74 mC, 52—220 received 1.5 mC, 52—221 received 3.3 mC, and 52—222 received 2.6 mC. They were put on the same study regime as the litter injected with radioactive iron in 1950 and when injected were about six months old, the same age as the first litter. The

rib biopsies on these latter dogs were done two and a half years after the injection of radioactive iron. Attempts to raise puppies of 52—222 the only female in this litter, were not successful.

The second litter was also sacrificed in November 1956 by pentobarbital sodium four and a half years after the iron injections. One dog from this litter, 52—220 had died two months after injection. No cause of death was found at autopsy.

### Observations

When the females became adult (one year or more in age) they were interbred with treated male 50—3, or control male 50—5, on several occasions in an attempt to study the second or third generation anomalies that might develop, 50—1 as an example was mated on March 28 1951, to dog 50—5. About 7 weeks later her weight was 36.4 lbs and five days later she delivered two live pups, two days after delivery her weight was 30.0 lbs. Her weight on October 8, 1951 was 36.0 lbs at which time she was mated with 50—3. On December 8 1951 five pups were born of which one was dead at delivery. Three days later the weight was 34.7 lbs. At this time, due to an anemia suspected to be on a basis of repeated pregnancy, injections of 100 mg equivalent of elemental iron in the form of 'Feojectin' (supplied through the courtesy of Smith Kline and French Co) were made on each of two days. Two weeks later 80 mg of iron equivalent in the form of ferrous gluconate (kindly supplied by Dr Georg Cronheim of the Massengill Co) were administered on each of two successive days. Litter mates including the control and the treated male received the same treatment. Of the pups born in December 1951 all had died by March 16, 1952 except one female. The surviving animal was retired to the country to insure survival and was subsequently returned to the laboratory and mated.

Animal 50—1 continued in good health with gradually increasing weight for the next several years. On January 23, 1955 her weight had reached 46.0 lbs and at this time a rib biopsy was obtained.

It will be noted that at no time except during the post partum period of November 28, 1951 to January 29 1952, was there any anemia and this responded very well to the intravenous administration of iron compounds. Otherwise there were neither periods involving leucopenia nor notable changes in the differentials, 50—1 remained in an excellent state of health and on November 29 1956 having a weight of 49 lbs was sacrificed for the study of various organs.

At autopsy (gross and microscopic examinations were carried out by Drs L. L. Miller and Thomas Harwood) the subcutaneous tissues and body cavities were normal in appearance. The skeletal muscle was a rich deep red color as was the shed blood. The parenchymatous organs and the body cavities were unremarkable. Sections of bone marrow through the shafts of four or five ribs showed it to be rather spotty with more than the usual amount of fat. The femoral and humeral epiphyses upon section showed only a greasy colorless



surface with prominent bony trabeculae. The vertebral marrow was moderately cellular. Histologically the rib biopsy, taken on January 23rd, 1955, was normally cellular with all hematopoietic series well represented. The autopsy histologic material, in two sections of the spleen, showed somewhat smaller than normal malpighian corpuscles. Occasional focal accumulations of golden yellow pigment were noted chiefly in the areas of the red pulp. The liver was of entirely normal architecture. The pancreas and kidney were essentially normal, as were the adrenal gland, thyroid and parathyroid. The aorta showed no remarkable changes. Lymph nodes from the pulmonary hilar region were unremarkable, except for dense accumulation of deep brown black pigment seen chiefly in the medullary phagocytic cells. A section of ovary revealed normal follicle development with a regressing corpus luteum. Autopsy of bone marrow, in sections of the femoral and humeral epiphyses, was without note, the marrow cavities being replaced nearly entirely with fatty areolar tissue. Rib sections taken from the costochondral areas showed various degrees of fitness. Other areas, however, were normally cellular with all hematopoietic series well represented. Two sections of vertebral bodies revealed normally cellular bone marrow.

The above description is essentially the same in all particulars as related to histories and autopsy findings of dogs 50-2 and 50-3, as also of dog 50-5 which was the control animal in this group.

Dog 50-2, which died a few hours after a caesarian section, was delivered of several dead pups. The section was performed because of an over due pregnancy three years after the original injection. Dog 50-3, a male, died after a rib biopsy taken on January 23, 1955 and death was attributed to a pneumothorax. Otherwise, his clinical history and autopsy findings were the same as those of the other dogs in the litter.

The second litter of animals, injected with variable amounts of the  $^{59}\text{Fe}$ , although studied for slightly shorter periods, showed essentially the same normal growth and development as did the first litter studied. Hematologic studies during life were normal. At time of sacrifice the remaining dogs of this litter, just as in the first group of dogs, showed no gross or histological changes that were felt to be significant. It should be noted that this second litter received much higher doses of iron radioactivity than the first group of dogs — as much as six times on a  $\mu\text{Ci/kg}$  basis in the case of one animal.

In general it is concluded that the mortality of the treated animals which did not survive, as well as that of their progeny resulting from inbreeding, was probably in all cases unrelated to any effects from months of irradiation derived from a high titre of  $^{59}\text{Fe}$  in the circulation.

### Discussion

We do not have figures available as to the half path in tissues of the very soft beta particle of the isotope used. It is difficult to even hazard a guess as to

how many cell diameters such beta particles might traverse before causing ionization. On the one hand it might be felt that most of the radiation effect would be accomplished within the confines of the vascular system. However in some respects this could be construed to mean fairly general body irradiation with the possible exception of certain fatty tissues for instance. Again one must recognize the high degree of vascularity of the liver and spleen where temporary sequestration of red cells perhaps occurs, especially in some sinuses. Furthermore during several life cycles of the red cell the iron is certainly deposited in some elements of the hematopoietic system for matters of hours, or possibly days. However, from earlier work we are fairly well convinced that the re utilization of iron following destruction of hemoglobin and re incorporation into a new hemoglobin molecule is very rapid (1) (2).

We must not forget the fact that the greatest part of the retained isotope is in the erythrocyte which is a fairly specialized type of cell. Having no nucleus in its adult stage where the isotope is carried for a period of 120 days there is little reason for anticipating radiation changes in a cell which in itself is non reproductive. It has been estimated by MARINELLI, QUIMBY & HINE (3) that 24  $\mu\text{C}$  would probably represent a safe level in the red cell mass of a human donor. The amounts used in these experiments would thus represent many hundred times as much radioactivity.

With the present state of knowledge of radiobiology it would be pure speculation to go further in an attempt to determine the lack of radiation effects in the animals studied here.

## SUMMARY

Two groups of litter mate dogs were injected with iron containing the  $^{59}\text{Fe}$  isotope at levels ranging from 0.74 to 3.3 mC (70 to 435  $\mu\text{C/kg}$ ) during active growth. The animals were followed for periods of four and a half to six years respectively. Complete blood examinations being conducted at monthly intervals. They developed normally and showed no clinical or hematologic changes up to the time of sacrifice.

## ZUSAMMENFASSUNG

Zwei Gruppen von jungen Hunden je vom selben Wurf erhielten Eisen-Einspritzungen von  $^{59}\text{Fe}$  in Dosen von 0.74 bis 3.3 mC (70 bis 435  $\mu\text{C/kg}$ ) während ihrer Wachstumsperiode. Die Tiere wurden über einen Zeitraum von 4 1/2 bis zu 6 Jahren mittels monatlichen Blutuntersuchungen beobachtet. Die Hunde erwiesen sich als normal und zeigten keine klinische oder hämatologische Veränderungen während ihres Lebens.

## RÉSUMÉ

Deux groupes de jeunes chiens de la même portée ont reçu au cours de leur croissance une injection de fer contenant une dose de l'isotope  $^{59}\text{Fe}$  comprise entre 0.74 et 3.3 mC (70 à 435  $\mu\text{C/kg}$ ). Ces animaux ont été observés pendant des périodes allant de quatre ans et demi à six ans subissant un examen hématologique complet tous les mois. Ils se sont développés normalement et n'ont présenté aucune anomalie clinique ni hématologique jusqu'au moment où ils ont été sacrifiés.

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## DETERMINATION OF INTEGRAL ABSORBED DOSE FROM EXPOSURE MEASUREMENTS

by

CARL CARLSSON

The integral absorbed dose (for brevity the term 'absorbed' will usually be omitted) is defined as the mass integral of the absorbed dose, integrated over the total body, or simply as the energy absorbed by the body during radiation treatment or examination

$$\Sigma = \int_M D \, dm \quad (1)$$

where  $\Sigma$  is an integral absorbed dose  $D$  absorbed dose  $M$  the total mass and  $dm$  is a mass element

If the mass is measured in gram and the absorbed dose in rad the integral dose will be expressed in g rad units  $1 \text{ g rad} = 100 \text{ erg} = 10^{-4} \text{ joule}$

(The names and symbols for radiation quantities and units used in this work have been chosen according to ICRU 'Radiation quantities and units 1962')

According to the definition the integral dose can be computed from measurements of the absorbed dose by several detectors uniformly spread throughout the body. This measurement naturally cannot be performed in man but with a convenient phantom this and other methods can be used to calibrate an external measuring instrument. A large plane parallel ionization chamber is often used (REINSMAN 1962, ARNAL & PYCHLAU 1961, ZIEGLER 1960, CARLSSON). The chamber is placed between the adjustable diaphragm of a roentgen tube and the patient and measures in the absence of a scattering medium the product

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of the exposure in air and the field area (more exactly the field integral of the exposure in air)

Methods for calculating integral doses from known exposure and field area have been derived by many authors. MAYNEORD (1940) attacked the problem in two ways: first by depth dose measurements in a phantom and secondly by calculating the incident radiation energy from known energy absorption coefficients for air and measured values of the exposure and field area. In the following, these two methods will be further analyzed.

### **I Calculation of integral absorbed dose from depth-dose measurements**

Measurements according to the definition of the integral dose have been made by MAYNEORD & CLARKSON (1944). They determined integral doses in a man equivalent phantom built of wax and rice, in which several ionization chambers were placed. BOAG (1945) used a man shaped phantom, the celluloid man. This consists of several plane parallel ionization chambers in which the electrodes also function as phantom material. The same phantom was also used by BEWLEY et al. (1959) in determining the integral doses from 200 kV and 8 MV radiation. The celluloid man obviates the time consuming work of constructing isodoses or adding many products of mass and absorbed dose. Instead one has, among other things, to correct for the different incidence angles of the radiation (because of the lamination) and for the fact that the wall material (cellulose acetate) in the ionization chambers causes the sensitivity of the chamber to decrease at the lowest HVT (1 to 4 mm Al) which are of interest here. Chemical dosimeters are very satisfactory from the point of view of the definition integral but their applications are restricted considerably as they suffer from one or more of the following disadvantages: low sensitivity, great energy dependence, especially for low energy roentgen radiation and rigorous demands on the purity of the chemicals and vessels used.

To measure on the basis of eq. 1 as the cited authors have done, is free from objections in principle but is so laborious that one hesitates to use such a method to calibrate an outer detector for various filters, tube potentials, wave forms, field areas, and focus skin distances, especially as the uncertainty in the determination of the low dose rates outside the geometrical radiation beam can easily be great. As the dimensions of the phantom used do not correspond to all cases where determinations of integral doses are of interest, the above mentioned measurements had to be made with many different phantoms.

The energy losses in lateral scattering are relatively small (ZIELER 1961). According to BEWLEY et al. (1959) they reach about 8 per cent of the incident energy at a HVT of 1.8 mm Cu and a field diameter of 10 cm, if the phantom is a 23 cm high truncated water cone with a smallest diameter of 25 cm. They estimate the back scattered and the transmitted energies as 19 and 17 per cent,

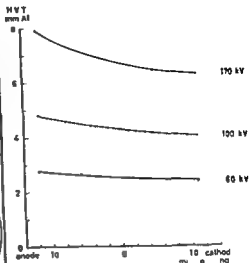
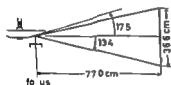
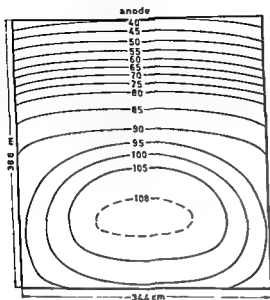


Fig 2

Fig 1 (left) Measured values for exposure in air from a diagnostic roentgen tube 75 kV and HVT = 4.3 mm Al

Fig 2 Variation of HVT with emission angle from a diagnostic roentgen tube

respectively. If this phantom is replaced by a water slab of the same thickness but with an infinite lateral extent, one part of the radiation losses through the sides of the cone will, after multiple scattering processes in the slab, appear as back-scattered or transmitted radiation, and the deviation will be less than the above-mentioned 8 per cent. The deviation will be still less at low HVT or if the edges of the field are more distant from the lateral limits of the phantom than in the above-mentioned example (this is generally valid in the longitudinal direction of the body when the trunk is irradiated). This idealized phantom (the water slab) opens the way to simplified calculations of the integral dose via central axis depth dose data and makes simple comparisons between different calculation methods possible. The thickness of the slab is of course easily variable. The well-known approximate formula of MAYNEORD (1940) estimates the integral dose via central axis depth dose data and integration over the geometrical beam. The drawbacks of this method may be overcome by always choosing the depth dose values for the calculations from very large fields (the saturated scatter method), independent of the size of the topical fields (HAPPEY 1940 and 1941; LOEFFLER 1956; SCARPA 1960). To elucidate this latter method, we may consider a small roentgen pencil, which is a part of and in the centre of

a large, uniform beam, incident on a large phantom. The field is so large that a further enlargement does not affect the central axis depth doses. The contribution from the small pencil to the integral dose is easily calculated by integrating the dose over that mass which is enclosed by the geometrical limitation of the pencil, as the energy that is lost by photons scattered out of this volume is just compensated by photons scattered in. If instead the same pencil alone irradiates the phantom, it will of course cause the same integral dose but this will be strongly underestimated by integrating the central axis depth doses over the mass within the volume of the pencil. The mass integral of the dose must instead be extended over the whole phantom to give the same result.

As, owing to radiation quality and phantom thickness, very large fields are often required to assure saturation of the scattered radiation at greater depths, it may be difficult to use the method. MEREDITH and NEARY (1944) have proposed a method of constructing isodose curves which makes it possible to extrapolate depth doses to infinite field areas. The method has only been applied for radiation qualities used in conventional roentgen therapy, and data are lacking for its application with radiation qualities common in diagnostic radiology. TROUT et al. (1952) have measured central axis depth doses for radiation qualities with HVT in the region 0.7 to 4.8 mm Al. These measurements were performed with a field having the dimensions  $36 \times 43$  cm<sup>2</sup>. Field dimensions and radiation qualities give rise to the presumption that these measurements could be used for calculating integral doses according to the saturated scatter method. However, it should be pointed out that the exposure rate from a lightly filtered diagnostic tube with small anode angle is far from homogenous over the whole field. An example of measurement of the distribution of the exposure in air from a diagnostic tube is shown in Fig. 1. The field dimensions and focus skin distance are about the same as given by TROUT. Apparently the exposure varies in the field by more than a factor of two. The integral  $\int A dA$  of the exposure,  $A$ , over the field area,  $A$ , calculated from Fig. 1 is 13 per cent less than if the whole field had been irradiated with the exposure of the central ray. With the aid of depth dose data for different field areas the dose contributions from scattered radiation from different parts of the field to the doses of the central ray can be calculated. From this it is possible to compute the effect of the exposure variations of the field on the doses of the central ray.

The integral doses calculated from central axis depth doses for an inhomogenous field (Fig. 1) and for a homogenous field with the same central axis dose at zero depth and with the same radiation quality have been compared, the calculated integral dose for the inhomogenous field is only about 3 to 4 per cent below that for the homogenous field. If consideration is taken of the fact that the radiation quality also depends on the direction, the difference will be still less. Fig. 2 shows how the HVT varies with the direction of the radiation along the axis of the roentgen tube, as measured by the author. Another serious

objection to using these depth dose measurements is that they have been made with a large ionization chamber (the Victoreen thimble chamber). The insertion of an air volume in the phantom material causes an increase in measured exposure because of the decreased filtration of both the primary and scattered radiation but also a diminished exposure contribution because of the elimination of scattered radiation from the displaced volume. This volume effect of the ionization chamber may lead to corrections in the measured depth doses by several per cent (LIDEN 1961, SKOLDBORN 1959). Usually a large ionization chamber causes an overestimate of the depth doses as well as of the integral dose calculated from them. The effects of an inhomogeneous field and a large ionization chamber may to a great extent cancel each other.

From the experimental values of TROUT *et al.* the author has calculated integral doses as follows:

$$\Sigma = \int_V D dm = \int_0^d \bar{f} \lambda \rho A_0 dx = \bar{f} \rho A_0 \int_0^d \lambda \left( \frac{F+x}{F} \right)^2 dx \quad (2)$$

where  $f = f$  factor = the ratio between the absorbed dose and the exposure for monoenergetic photons in water.

$\bar{f}$  = the average value of the  $f$  factor for the photon spectrum in the phantom. The values of  $\bar{f}$  have been taken from National Bureau of Standards Handbook 78 (1961) and are given in Table 1.

$\lambda$  = the exposure in the central ray at the depth  $x$ .

$\rho$  = the density of the phantom material.

$A_0$  = surface area of the field.  $A$  = the field area at the depth  $x$ .

$F$  = focus-skin distance.

$x$  = the depth in the phantom.

If  $\lambda$  is expressed as a fraction of the exposure measured in the centre of the beam at the position of the phantom surface but with the phantom removed, if  $A_0$  is chosen as 1 cm<sup>2</sup> and if the phantom material has the density 1 g/cm<sup>3</sup>, eq. 2 may be simplified to

$$\Sigma = \bar{f} \int_0^d \lambda \left( \frac{F+x}{F} \right)^2 dx \text{ g rad/(cm}^2 \text{ R)} \quad (3)$$

This integral has been evaluated for  $d = 20$  cm for fifteen cases with HVT between 0.91 and 4.8 mm Al. The results are presented in Table 1 in the column  $\int_0^d$ . For the calculation of

$\lambda$  according to the method of MEREDITH & VARY, the contribution from the primary radiation has been taken from depth dose values for zero area (Depth Dose Tables for Use in Radiotherapy 1961) and the saturated scatter from HORSELEY & ASPRY (1956).

As earlier, the integral

$$\Sigma = \bar{f} \int_0^d (P + M) \left( \frac{F+x}{F} \right)^2 dx \quad (4)$$

was determined graphically (the results being given in Table 1 for  $d = 20$  cm).  $P$  = exposure from the primary radiation.  $M$  = saturated scatter, both are expressed as fractions of the primary exposure at zero depth.

Eqs 3 and 4 are approximately independent of the focus-skin distance. For a semi-infinite phantom, the integral dose per cm<sup>2</sup> and R will be slightly less for a shorter focus-skin distance (even if the exposure is constant over the whole surface) owing to the fact that the backscattered energy increases with the obliquity of the incident rays (BERGER & RASO 1960).



Table 1

Integral dose and fractional transmission calculated from depth dose values

	kV	Added filter mm	HVT measured mm	$\frac{2d}{f}$	$\int_0^\infty \bar{f} = \Sigma_{\infty}$	$\Gamma_{10}$	$\Sigma_{10}$	$\Sigma_{25}$
				g rad cm <sup>-2</sup> R <sup>-1</sup>				
TROUT et coll	85	0 Al	0.91 Al	4.9	5.0	0.1	4.2	4.7
	85	0.5 Al	1.35 Al	6.0	6.0	0.2	4.7	5.5
	85	1.0 Al	1.54 Al	6.9	7.2	0.3	5.5	6.5
	85	2.0 Al	1.95 Al	8.2	8.6	0.5	6.3	7.5
	85	3.0 Al	2.50 Al	9.2	9.8	0.8	7.0	8.3
TROUT et coll	100	0 Al	1.00 Al	6.7	7.2	0.7	4.9	6.0
	100	0.5 Al	1.60 Al	7.7	8.2	0.7	5.7	6.9
	100	1.0 Al	1.95 Al	8.9	9.6	0.9	6.5	7.9
	100	2.0 Al	2.90 Al	10.6	11.8	1.5	7.4	9.2
	100	3.0 Al	3.60 Al	11.9	13.2	1.6	8.1	10.3
TROUT et coll	150	0 Al	1.20 Al	7.4	7.9	0.6	5.3	6.6
	150	0.5 Al	1.95 Al	9.3	10.3	1.2	6.4	8.0
	150	1.0 Al	2.90 Al	10.8	12.1	1.7	7.2	9.7
	150	2.0 Al	4.1 Al	12.4	14.1	2.1	8.1	10.6
	150	3.0 Al	4.8 Al	13.6	16.2	3.2	8.4	11.2
MEREDITH NEARY	—	—	0.5 Cu	17.3	21.1	4.8	9.6	13.7
	—	—	1.0 Cu	20.4	26.6	7.6	10.1	15.3
	—	—	2.0 Cu	20.9	28.2	9.1	9.6	15.7
	—	—	3.0 Cu	20.2	28.7	10.6	8.8	14.2
	—	—	4.0 Cu	18.8	27.8	11.3	7.8	12.8

$\Sigma_d$  means integral dose per cm<sup>2</sup> and R in a  $d$  cm thick water slab  $\int_0^d \bar{f} dx \left( \frac{F+x}{F} \right)^2 dx$  See eqs (3) and (4)

The results  $\Sigma$  are corrected for errors in depth doses owing to the fact that they are measured in a phantom thicker than  $d$  cm.  $T_d$  means energy transmitted per incident cm<sup>2</sup> and R.

$\frac{T_d}{E_f}$  means fraction of the incident energy which is transmitted through a  $d$  cm thick water slab

In a water slab with finite thickness the transmission decreases with shorter focus skin distance owing to the longer path in the phantom. These phenomena are however of small importance at ordinary focus skin distances, and as they mainly refer to the boundary rays they have only a small effect on the central axis depth doses and the integral dose calculated from them.

Therefore eqs 3 and 4 may be evaluated most easily with depth doses measured as tissue air ratios. The tissue air ratio is independent of the focus skin distance and equivalent to the infinite focus skin distance in eqs 3 and 4 (JOHNS et coll 1958)

Fig 3 gives for roentgen radiation of HVT = 0.5 mm Cu the central axis

Table 1 (cont.)

$\Sigma$	$\Sigma_{11}$	$\Sigma_{22}$	$\frac{T}{\Sigma_{\infty}}$	$\frac{T}{E_f}$	$\frac{T_{15}}{E_f}$	$\frac{T}{E_f}$	$\frac{T}{E_f}$	$\frac{T_{22}}{E_f}$	$A_{E_0}$	$\bar{f}$ rad R
g rad cm <sup>-2</sup> R <sup>-1</sup>										
49	50	50	0.018	0.13	0.04	0.014	0.004	0.001	0.23	0.932
58	59	60	0.034	0.16	0.07	0.076	0.010	0.004	0.23	0.937
69	70	71	0.046	0.18	0.08	0.035	0.016	0.007	0.23	0.932
81	84	85	0.053	0.21	0.10	0.048	0.023	0.011	0.23	0.932
90	94	96	0.078	0.22	0.12	0.060	0.031	0.016	0.23	0.932
66	69	70	0.091	0.24	0.13	0.070	0.037	0.020	0.24	0.937
76	79	81	0.084	0.24	0.13	0.064	0.037	0.017	0.24	0.937
87	92	94	0.091	0.25	0.13	0.069	0.036	0.018	0.24	0.932
103	109	113	0.13	0.28	0.17	0.10	0.058	0.035	0.24	0.932
116	123	127	0.12	0.29	0.16	0.090	0.050	0.028	0.24	0.932
73	76	78	0.08	0.25	0.13	0.06	0.028	0.013	0.24	0.932
90	96	99	0.12	0.29	0.17	0.09	0.050	0.027	0.24	0.932
105	112	116	0.14	0.31	0.18	0.10	0.059	0.034	0.24	0.937
120	128	133	0.15	0.32	0.19	0.11	0.068	0.040	0.24	0.932
130	141	148	0.20	0.36	0.23	0.15	0.098	0.063	0.24	0.932
163	180	191	0.23	0.41	0.26	0.17	0.11	0.07	0.25	0.94
189	213	230	0.29	0.47	0.32	0.22	0.15	0.10	0.25	0.95
191	218	237	0.32	0.49	0.34	0.24	0.17	0.12	0.25	0.95
181	210	230	0.37	0.53	0.39	0.28	0.21	0.16	0.23	0.96
165	193	215	0.41	0.57	0.43	0.32	0.24	0.18	0.21	0.96

depth exposure  $\lambda$ , expressed as a fraction of the incident exposure in air and multiplied by the factor  $\left(\frac{F+x}{F}\right)^2$  as a function of the depth in water. The expression  $\left(\frac{F+x}{F}\right)^2 dx$  constitutes a volume element with the incident area = 1 cm<sup>2</sup>. The integral  $\int_0^d \lambda \left(\frac{F+x}{F}\right)^2 dx$  expresses a volume dose. Multiplication by the density of the phantom gives the integral absorbed dose per cm<sup>3</sup> and roentgen unit according to eq. 3.

According to the saturated scatter method the integral dose will be underestimated if the central axis depth doses do not have a saturated contribution of scattered radiation. The upper curve in Fig. 3 which was calculated according to MEREDITH & NEARY (infinite field area) meets the saturation conditions, and the area beneath the curve is a measure of the integral dose. The other curves which refer to depth doses from finite fields underestimate the integral dose to an increasing extent as the field area and thus the contribution

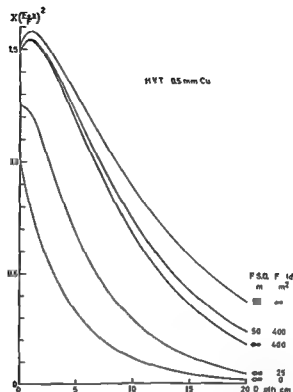


Fig 3 The integrand in eqs (3) and (4) Upper curve represents depth doses with a saturated scatter contribution The area beneath this curve is proportional to the integral dose For doses from a decreasing field area, eq (3) underestimates the integral dose to an ever increasing extent

of scattered radiation to the measured depth doses gradually decreases. In succession from top to bottom the different areas beneath the curves under estimate the integral dose by 12, 17, 53, and 75 per cent. Calculations of the integral dose based on depth dose values and integration over the geometrical cone of radiation can easily result in errors of a factor 2, and in extreme cases even a factor 4, if the saturation conditions are not fulfilled.

Of the two cases in Fig 3 with the same incident area (400 cm<sup>2</sup>) but different focus skin distances (50 cm and infinity), the field with the shorter focus skin distance best meets the saturation conditions since the field area in this case increases with the depth and the relative contribution of scattered radiation to a point at a depth  $x$  is dependent of the area of the field at this depth and is independent of the divergence of the radiation (JOHNS et coll 1958). MAYNEORD's well known and often applied formula differs from eq 3

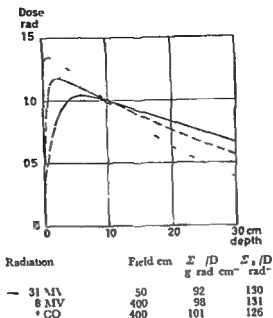


Fig 4 Ratio of integral dose to tumour dose for three radiation qualities

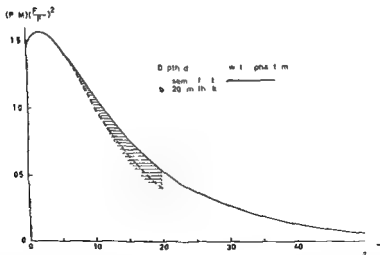


Fig 5 Depth doses in a semi infinite medium and in a 20 cm thick water slab. The crossed area corresponds to the energy scattered backwards through the 20 cm plane in the semi infinite medium. Of this energy a fraction is scattered forward over the same plane and so on. The broken curve gives the depth doses in the slab.

in the approximation of the depth dose as exponentially decreasing in order to obtain a definition integral which can be evaluated

This and similar methods therefore underestimate the integral doses in the same way as the graphical method presented here. This graphical method has besides greater accuracy the advantage of being easily applicable to high energy radiation where the dose is far from exponentially decreasing. For particle as well as photon radiation of sufficiently high energy the forward scattering dominates to the extent that saturation of the central axis depth doses will be reached for the moderate field areas reported in the standard tables. Fig. 4 gives a comparison of integral doses from  $^{60}\text{Co}$  8 and 31 MV roentgen radiation for the same tissue (tumour) dose at a depth of 10 cm. The dose values have been taken from tables for infinite focus skin distance ('Depth dose tables for use in radiotherapy, 1961'). It is seen that the 31 MV radiation gives the lowest and  $^{60}\text{Co}$  the highest integral dose for a 20 cm thick phantom. For a 30 cm thick phantom and the same tumour depth the  $^{60}\text{Co}$  radiation is preferable.

As the phantom used for the depth dose measurements is usually semi infinite or at least 30 cm deep, the measured depth doses will be larger than if they had been measured in a phantom with smaller dimensions. This is because one part of the dose contribution in the measurement in the thicker phantom originates from radiation that has been backscattered from deeper parts of the phantom. If the integrand  $\tilde{f}\left(\frac{r+x}{R}\right)^2$  is extrapolated to infinite depth, i.e. by

supposing the whole expression to be exponentially decreasing and then integrated graphically, first over the actual depth 0 to  $d$ , and secondly integrated numerically from  $d$  to infinity, then the integral dose to the depth  $d$ , calculated in this way, can be corrected by considering the energy albedo. The energy albedo  $A_E$  is defined as the ratio between the reflected and the incident energy. Albedo values for semi infinite media of different materials have been calculated by the Monte Carlo method (BERGER & RASO 1960) for photon energies between 20 keV and 3 MeV and different incidence obliquities.

Fig. 5 gives one example of the integrand in eq. 4 in a semi infinite phantom (solid curve). The broken line refers to the same integrand measured in a phantom  $d$  cm thick. In the figures,  $d$  has been chosen as 20 cm because this thickness corresponds well with the mean value of the thickness of the trunk in the antero-posterior direction in adults. Of the energy  $T_d$  which is transmitted in a phantom of thickness  $d$ , the fraction  $A_{F1}$  is reflected if the depth of the phantom is increased to infinity. However the fraction  $A_F$  is backscattered from the first  $d$  cm of the phantom, and so on.  $A_{F1}$  is the mean energy albedo value determined from the energy and direction of the photons.

For the calculation of the transmitted energy  $T_d$  in a water slab of thickness  $d$  from dose values measured in a semi infinite phantom eq. 5 is valid (for brevity the integrand from eqs 3 and 4 is omitted)

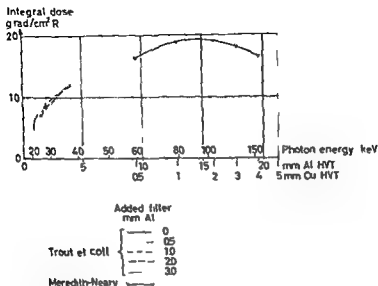


Fig. 6 Calculated integral doses in a 20 cm thick water slab as a function of the HVT in mm Al

$$f_d^\infty = T_d - A_E T_d + A_E A_E T_d - A_E A_E A_E T_d + \dots \quad (5)$$

This series converges rapidly because  $A_E$  as a rule is smaller than 0.3. In the calculations all  $A_E$  have been chosen equal to  $A_E = A_E = 0.25$ . This gives

$$f_d^\infty = T_d \sum_{n=0}^{\infty} (-A_E)^n \quad \text{or} \quad T_d = (1 + A_E) f_d^\infty \quad (6)$$

The corrected integral dose is then

$$\Sigma_d = \Sigma_{\infty} - T_d \quad (7)$$

Eqs 6 and 7 have been solved for different  $d$  and are shown in Table 1. The transmission is then expressed as a fraction partly of the integral dose in a semi infinite phantom  $\left( \frac{T_d}{\Sigma_{\infty}} \right)$  and partly of the incident energy  $\left( \frac{T_d}{E_f} \right)$ . The transmitted and incident energy are here normalized to 1 cm² R incident. The incident energy fluence per roentgen unit [erg (cm² R)] is obtained from the relation  $\Sigma_{\infty} = E_f (1 - A_E)$  (8)

where the energy albedo  $A_E$  of the primary radiation denotes the fraction of energy back scattered from the phantom surface.  $A_E$  is obtained from the spectral calculations described under next heading and from Table 1.

On the basis of the values in Table 1, the integral doses in a 20 cm thick phantom are presented in Fig. 6 as a function of HVT in mm Al. The other two

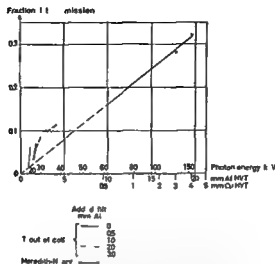


Fig 7 Fraction of the energy transmitted through a 20 cm thick water slab. The lower the filtration the higher the transmission for low HVT

scales HVT in mm Cu and keV, are both related to the first scale in a manner that is valid for monoenergetic photons. Fig 7 presents in the same way the transmission through a 20 cm thick water phantom. For low HVT a tendency to higher integral dose and transmission can be seen for lightly filtered radiation. This is due to the fact that the HVT in these cases underestimates the average energy of the radiation. We shall return to this question in the following.

## II Calculation of the integral absorbed dose by determination of the incident energy

The incident energy can be measured directly by calorimetric methods. Simultaneous measurement of the exposure allows the determination of the energy fluence necessary to give one roentgen in free air. The expression energy fluence means the time integral of the energy flux density and has the dimension energy per area (ICRU 1962). A calorimetric determination of the energy fluence per roentgen unit with the radiation qualities in which we are interested here has been reported by LAUGHLIN & GENVA (1956). They used roentgen apparatus with potentials between 130 and 400 kV and HVT between 5.1 mm Al and 3.0 mm Cu (see Table 2 and Fig 8).

Measurements of spectra of primary roentgen radiation, which have been reported by, among others, CORWACK et al. (1958 and 1960) and HETTINGER & STARIFLT (1958) also give the incident energy. These measurements were performed with scintillation spectrometers with various acceleration potentials

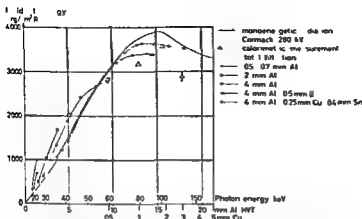


Fig 8 The energy fluence per R for different filtered radiations as a function of the radiation quality. For 140 kV radiation with a total filtration of 0.6 mm Al the data for monoenergetic radiation with the same HVT underestimates the incident energy by a factor of 3.

and filters in the roentgen apparatus. Simultaneous measurements of the exposure were not reported, which explains why the experiments do not directly give the energy fluence per roentgen unit. These measurements were performed with a very narrow beam geometry and with intensities so low that exposure measurements under the same conditions would be troublesome.

If the energy absorption coefficients for air and the average energy necessary to produce an ion pair in air are known, the energy fluence per roentgen unit can be calculated from

$$E_f = \frac{W}{\left(\frac{\mu_a}{\rho}\right)} \text{ erg cm}^{-2} \text{ R}^{-1} \quad (10)$$

where  $E_f$  is the necessary energy fluence to give 1 R in air,  $W$  is the average energy dissipated in air in forming one ion pair expressed in eV,  $\left(\frac{\mu_a}{\rho}\right)_a$  is the mass energy absorption coefficient for air ( $\text{cm}^2/\text{g}$ ).

$E_f$  as a function of the photon energy has been calculated by, among others, MAYNEORD (1940), JOHNS & LAUGHLIN (1956) and MULVEY & BALLINGER (1961). The latter in their work use values of the absorption coefficient from WHITE GRIFFIN (1957) and their calculations are used in the following. However, 34 eV will be preferred as a value of  $W$  instead of the value 33 eV used by MULVEY & BALLINGER (ICRU 1961). As it is assumed to be a constant over the whole energy interval this involves only a small correction. Newer values of the energy absorption coefficient (R. T. BERGER 1961) do not appreciably change the results given here.

The incident energy can then be calculated from eq. 10 if the field area and the exposure in air are measured, provided that the photons are monoenergetic. By means of eq. 10 and measured spectra of primary roentgen radiation the energy fluence per roentgen unit can be calculated for radiation with a continuous spectrum.



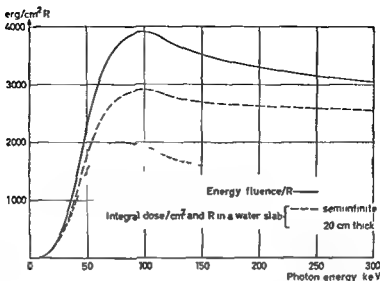


Fig. 9 The incident energy per  $\text{cm}^2$  and R (solid curve) as a function of the photon energy. For the broken curve the reflected energy is subtracted from the incident. For the dotted curve the transmitted as well as the reflected energies are subtracted.

If  $\epsilon$  is the energy of the photons  $P(\epsilon)$  the number of normally incident photons with the energy  $\epsilon$  per keV interval and  $\text{cm}^2$  then  $P(\epsilon) d\epsilon$  expresses the number of incident photons per  $\text{cm}^2$  with energies between  $\epsilon$  and  $\epsilon + d\epsilon$ .  $\epsilon P(\epsilon) d\epsilon$  erg/ $\text{cm}^2$  expresses the energy fluence of these photons.  $\frac{\epsilon P(\epsilon) d\epsilon}{E_f(\epsilon)}$  expresses the exposure in air which this energy fluence gives.

The mean value of the energy fluence per roentgen unit for the whole spectrum is given by

$$\bar{E}_f = \frac{\int_0^{\infty} \epsilon P(\epsilon) d\epsilon}{\int_0^{\infty} \frac{\epsilon P(\epsilon) d\epsilon}{E_f(\epsilon)}} \quad (11)$$

In the calculation of eq. 11,  $E_f$  as already mentioned, has been taken from MULVEY & BALLINGER with  $W = 34$  eV. The spectral distributions were first obtained from measured primary spectra (HETTINGER & STARFELT, COR MACK et coll.) and then by calculating new, more heavily filtered spectra from the first mentioned. Instead of  $P(\epsilon)$ ,  $P(\epsilon)e^{-\mu(\epsilon)d}$  is inserted in eq. 11, where  $\mu(\epsilon)$  = the total linear attenuation coefficient for the filter material,  $d$  = the linear thickness of the filter,  $\mu(\epsilon)$  has been taken from WHITE GROSSSTEIN (1957). Coherent scattering is also included in  $\mu(\epsilon)$ . This is reasonable on account of the extreme narrow beam geometry in the spectral measurements.

Filter materials and thicknesses have been chosen so that the resulting total

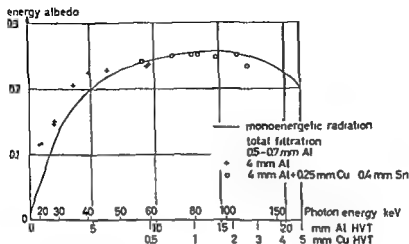


Fig 10 The energy albedo for monoenergetic photons and for roentgen radiation of different filtration

filters (inherent and added) amount to 2 3 and 4 mm Al 4 mm Al + 0.5 mm Cu, and 4 mm Al + 0.25 mm Cu + 0.4 mm Sn. The calculations cover radiation qualities used both in roentgen diagnostic examinations and in radiotherapy. For each of these spectra  $E_f$ , the energy fluence per roentgen unit and also the half value thickness or half value layer (HVT or HVL), have been calculated for both mm Al and mm Cu. HVT is here, as in the preceding section, defined as the thickness of an attenuator which is necessary to reduce the exposure or the exposure rate in air by a factor of two. In the calculations of the HVT the same absorption coefficients have been used as in the spectral calculations. The HVT is obtained from

$$\frac{1}{2} \frac{\int_0^\infty \epsilon P(\epsilon) d\epsilon}{\int_0^\infty \frac{\epsilon P(\epsilon)}{E_f(\epsilon)} d\epsilon} = \int_0^\infty \frac{\epsilon P(\epsilon) e^{-\mu(\epsilon) \text{HVT}} d\epsilon}{\int_0^\infty \frac{\epsilon P(\epsilon)}{E_f(\epsilon)} d\epsilon} \quad (12)$$

In practice instead of HVT different thicknesses,  $d$ , are tried in eq 12 so that the ratio between the integrals gives values in the neighbourhood of 0.5. Then HVT is obtained by interpolation, i.e. just as in HVT measurements. For measurements of HVT defined as in eq 12 a stringent narrow beam geometry is necessary.

Fig 11 shows both  $E_f$  and  $E_r$  (monoenergetic photons) as functions of HVT in mm Al. The curve without signs corresponds to monoenergetic radiation and the other curves correspond to roentgen radiation with the indicated total filtration. The lowest HVT corresponds to the lowest voltage of the roentgen tube. Specifications of voltages are given in Table 2. As could be expected, the curves for heavily filtered radiation (narrow spectrum) agree best with the curve for monoenergetic photons. The greatest deviations are found with light filtrations and tube voltages of about 100 kV.

Of course the maxima of the curves for the spectra are inferior to that of the monoenergetic radiation. This explains why  $\bar{E}_f < E_f$  for HVT greater than 0.5 mm Cu. For low HVT,  $\bar{E}_f > E_f$ , especially at low filtrations. In this case, for the HVT measurement of radiation with a broad spectrum, the exposure is reduced to one half mainly by a strong absorption of low energy photons. These low energy photons provide a large contribution to the exposure but a small contribution to the energy fluence, and therefore the spectrum is allotted an effective energy (its HVT) lower than its energy fluence and mean energy would indicate.

From a knowledge of the total filtration the incident energy can be calculated by means of Fig. 8 if the exposure in air and the field area are known. As seen in Fig. 8, the agreement between the calorimetric measurements of the energy fluence per roentgen unit and the spectral calculations is surprisingly good in the cases where direct comparisons can be made (130 kVp and 4.1 mm Al total filter and 250 kVp and 0.5 mm Al + 1.5 mm Cu total filter). Also in the other cases the same general trends are to be found as in the spectral calculations: i.e. the broader the spectrum the greater the deviations from the monoenergetic curve.

The integral dose is obtained from the incident energy by subtraction of backscattered and transmitted radiation energy.

The fraction of the energy scattered backwards is taken from the energy albedo calculations of BERGER and RASO (1960) and the fraction of the energy transmitted from the calculations in section I. Fig. 9 gives for monoenergetic radiation (a) the energy fluence per roentgen (b) the integral dose in a semi-infinite water medium (backscattered energy subtracted from (a)) (c) the integral dose in a 20 cm thick water slab (the transmitted energy subtracted from (b)).

The integral doses and the backscattered and transmitted energies in (b) and (c) are per cm<sup>2</sup> and roentgen unit. The transmission calculations are performed for continuous spectra and are not strictly valid for monoenergetic photons. As a further criticism may be mentioned that the backscattered energy from a water slab will be slightly overestimated because it has been calculated for a semi-infinite phantom. According to BERGER & DOGGETT (1956) the reflection from a barrier will rapidly assume its maximum value. A water slab with a thickness of two mean free paths of the primary photons (0.66 MeV) is already equivalent to a semi-infinite medium. LEIMDORFER (1963) has shown that to reach the maximum value of reflected energy in concrete a greater thickness in mean free paths is required at lower photon energies in the range 1 to 10 MeV. From backscatter measurements by HETTINGER (1960) it is evident that at least 3 mean free paths are necessary at photon energies as low as between 60 and 100 keV. A mean free path (mfp) in water is for 60 keV photons 4.9 cm and for 200 keV photons 7.3 cm. Then the 20 cm thick water slab is at least 3 to 4 mfp for most of the spectra considered here. The

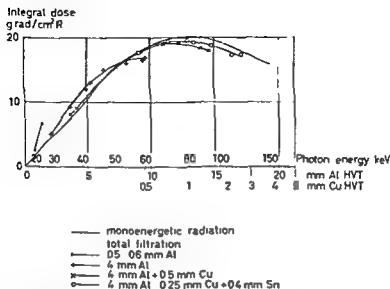


Fig. 11 Integral doses per cm<sup>2</sup> and R in a 20 cm thick water slab as a function of the radiation quality

overestimate of the reflection in the calculations is then slight and only at the highest energies may one expect slightly underestimated integral doses

For all the spectra in Table 2 a mean energy albedo  $\bar{A}_E$  has been calculated as

$$\bar{A}_E = \frac{\int_0^\infty A_E(\epsilon) \epsilon P(\epsilon) d\epsilon}{\int_0^\infty \epsilon P(\epsilon) d\epsilon} \quad (13)$$

In Fig. 10 both  $A_E$  (monoenergetic photons) and  $\bar{A}_E$  for the different filtered radiation are presented as functions of the HVT in aluminium. The reflected and transmitted energies have been subtracted from the incident energy from the different spectra according to

$$\Sigma = \frac{\int_0^\infty [(1 - A_E - T_E) \epsilon P(\epsilon) - T_E \epsilon] d\epsilon}{\int_0^\infty \frac{\epsilon I(\epsilon) d\epsilon}{E_f(\epsilon)}} \quad (14)$$

The results integral doses in a 20 cm thick water slab are presented in Table 2 and Fig. 11

### III Comparison between different estimations of integral doses

From Fig. 12 which is a combination of Figs. 6 and 11 calculations of integral doses from depth dose data and primary spectra can be compared. From both methods it is obvious that the HVT concept measured in mm Al

Table 2

*Integral dose calculations from spectral measurements*

Spectrum (The term calculated means calculated by the author from the measured spec- trum ~ means alternating voltage)		kV	Total filtration mm	HVT	
				Calculated	
				mm Al	mm Cu
HETTINGER STARFELT	measured	45	0.7 Al	1.00	0.030
	calculated	45	2.0 Al	1.50	—
	»	45	3.0 Al	1.80	—
	»	45	4.0 Al	2.04	0.041
	»	45	4 Al + 0.5 Cu	3.65	0.13
	»	45	4 Al + 0.25 Cu + 0.4 Sn	2.06	0.081
HETTINGER STARFELT	measured	75	0.7 Al	1.35	0.047
	calculated	75	2.0 Al	2.46	—
	»	75	3.0 Al	3.06	—
	»	75	4.0 Al	3.58	0.14
	»	75	4 Al + 0.5 Cu	7.33	0.37
	»	75	4 Al + 0.25 Cu + 0.4 Sn	9.09	0.40
HETTINGER STARFELT	measured	100	4 Al	4.90	0.143
	calculated	100	4 Al + 0.5 Cu	9.3	0.30
	»	100	4 Al + 0.25 Cu + 0.4 Sn	11.4	0.37
HETTINGER STARFELT	measured	145	4 Al	6.33	0.304
	calculated	145	4 Al + 0.5 Cu	11.0	0.743
	»	145	4 Al + 0.25 Cu + 0.4 Sn	13.4	1.1
HETTINGER STARFELT	measured	170	4 Al	8.13	0.46
	calculated	170	4 Al + 0.5 Cu	12.2	1.00
	»	170	4 Al + 0.25 Cu + 0.4 Sn	14.8	1.43
HETTINGER STARFELT	measured	225	4 Al	9.60	0.68
	calculated	225	4 Al + 0.5 Cu	13.9	1.44
	»	225	4 Al + 0.25 Cu + 0.4 Sn	16.4	2.27
HETTINGER STARFELT	measured	250	4 Al	9.44	0.646
	calculated	250	4 Al + 0.5 Cu	14.6	1.66
	»	250	4 Al + 0.25 Cu + 0.4 Sn	17.1	2.64
HETTINGER STARFELT		50~	0.7 Al	0.74	0.092
	calculated	50~	4.0 Al	1.87	0.057
	»	50~	4 Al + 0.5 Cu	3.76	0.13
HETTINGER STARFELT		90~	0.7 Al	1.33	0.04
	calculated	90~	4.0 Al	3.49	0.12
	»	90~	4 Al + 0.5 Cu	7.67	0.35

Table 2 (cont.)

HVT	Energy fluence per roentgen erg cm <sup>-2</sup> R <sup>-1</sup>	Energy albedo per cent	Phantom 90 thick	
			Transmiss on per cent	Integral dose per cm and roentgen g rad cm <sup>-2</sup> R <sup>-1</sup>
—	322	11.7	3.4	3.00
—	488	13.3	4.0	4.04
—	567	14.1	4.3	4.60
—	672	14.7	4.6	5.00
—	1070	18.4	6.8	8.00
—	599	13.7	4.4	4.90
—	690	17.9	5.1	5.15
—	1030	19.6	9.4	7.30
—	1200	20.4	10.3	8.30
—	1340	20.6	10.6	9.30
—	2410	23.9	12.8	15.4
—	2910	24.2	15.0	17.7
0.19 Cu	1890	22.5	13.0	12.1
—	2970	24.3	15.8	17.8
—	3440	25.0	18.7	19.4
0.30 Cu	2420	22.8	15.2	15.0
—	3280	24.8	17.4	18.9
—	3650	25.7	22.0	19.7
0.39 Cu	2670	23.9	16.7	15.9
—	3370	24.7	18.6	19.1
—	3630	24.8	24.0	18.6
0.50 Cu	2850	23	17.2	16.9
—	3470	24.1	22.3	18.3
—	3580	2	26.6	17.3
0.69 Cu	2700	2	1.7	16.5
—	3390	23.7	23.4	1.9
—	3540	23.4	27.5	1
—	70	10.5	3.1	3.3
—	83	14.1	4.1	4.76
—	1040	18.6	6.6	8.14
—	10	18.1	8.7	4.94
—	1360	27.5	9.9	9.70
—	2570	23.5	13.2	15.9

Table 2 (cont.)

Spectrum		kV	Total filtration mm	HVI	
				calculated	
				mm Al	mm Cu
CORMACK	measured	110	0.1 Al	1.33	0.03
	calculated	110	2.0 Al	3.75	
	"	110	3.0 Al	3.62	
	"	110	4.0 Al	3.30	0.23
	"	110	4 Al + 0.3 Cu	10.3	0.17
	"	110	4 Al + 0.2 Cu + 0.1 Sn	12.3	1.10
CORMACK*	measured	140	0.6 Al	1.33	0.0
	calculated	110	1.0 Al	5.17	0.24
	"	140	1 Al + 0.3 Cu	10.3	0.1
	"	110	4 Al + 0.2 Cu + 0.1 Sn	12.9	1.10
CORMACK	measured	210	2 Al + 0.2 Cu + 0.2 Sn	13.3	1.7
	"	280	2 Al + 0.2 Cu + 0.6 Sn	17.1	2.17
	"	280	2 Al + 0.3 Cu + 1.2 Sn	18.1	3.10
	"	280	2 Al + 0.3 Cu + 1.2 Sn	18.1	3.10
FURTH	measured	30	0.3 Al	0.77	0.03
	calculated	30	4.0 Al	2.03	0.03
	"	30	4 Al + 0.3 Cu	1.11	0.114
	"	30	4 Al + 0.2 Cu + 0.1 Sn	2.33	0.03
FALMIN calculator	measured	110~	1.1 Al		
	"	200~	0.1 Al + 0.3 Cu		
	"	250~	0.1 Al + 0.3 Cu		
	"	300~	0.3 Al + 1.3 Cu		
	"	100~	1 Al + 2.0 Cu		

\* In the calculation of  $\left(\frac{\mu}{\rho}\right)_1$  in eq. 10 is taken from R. L. BARNER (1961)

does not correspond to a unique integral dose. As in Figs 6, 7, 8 and 11, Fig. 12 shows that the HVI underestimates the average energy of the spectrum in the low energy region.

The agreement between the results of the two calculation methods is rather good although in the low energy region 1 to 5 mm Al HVI, the depth dose calculations result in higher integral doses than the spectral calculations for the same HVI and filtration. As reasons for the deviations may be mentioned:

1. TROU ET COLL (1952) measured their depth doses with a load up to 500 mA of a full wave 60 cycle diagnostic roentgen unit, while the spectral measurements were performed with so low currents less than 1 mA, that the tube voltage owing to the influence of the cable capacitance (TROU ET COLL 1960) was constant. There probably are a relatively greater number of low energy photons in the radiation from a tube with pulsating voltage. This means that

Table 2 (cont.)

HVT Measured mm	Energy fluence per roentgen $\text{erg cm}^{-2} \text{R}^{-1}$	Energy albedo per cent	Phantom 20 cm thick	
			Transmission per cent	Integral dose per cm and roentgen $\text{g rad cm}^{-2} \text{R}^{-1}$
133 Al	995	21.3	12.0	6.63
—	1680	22.3	13.0	10.9
—	1850	22.8	13.4	12.1
—	2050	23.1	13.6	13.0
—	3200	24.6	16.8	18.8
—	3620	25.2	21.0	19.5
133 Al	1040	—	—	—
—	2130	—	—	—
—	3230	—	—	—
—	3590	—	—	—
177 Cu	3390	23.8	23.4	17.9
203 Cu	3530	23.5	27.5	17.3
314 Cu	3620	23.2	29.1	17.3
—	302	11.5	3.5	2.57
—	649	15.1	4.7	2.20
—	1230	19.3	7.4	2.00
—	724	16.8	5.8	6.06
51 Al	2020	—	—	—
05 Cu	2840	—	—	—
10 Cu	3170	—	—	—
19 Cu	3520	—	—	—
30 Cu	$2850 \pm 90$	—	—	—

the HVT underestimates to an even greater extent the average energy of the radiation, which may explain the whole deviation. In Table 2 a few spectra with pulsating tube voltage (HETTINGER & STARFELT) have been used for integral dose calculations. The expected higher integral dose per cm and roentgen unit than for radiation with the same HVT and filtration but with constant voltage has not been observed with certainty.

2. The relatively large ionization chamber used by TROUT et al. gives too high values in a phantom.

3. The spectral measurements underestimate the number of low energy photons. The number of low energy photons  $P(\epsilon)$  just is the energy fluence per roentgen unit  $E_{\gamma}(\epsilon)$  varies rapidly with the energy  $\epsilon$  for the lowest energies which explains the fact that the calculation of eq. 11 is most uncertain for low photon energies.



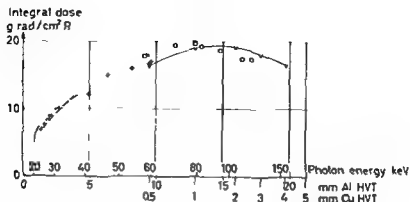


Fig. 13. Combination of figs 6 and 11. The integral doses calculated from depth doses and spectral measurements can be compared.

Integral doses calculated by means of the Meredith Neary method differ less than those based on FOURT et coll from the spectral calculations (Fig. 13). The method of Meredith Neary gives lower integral doses for HVI beneath 1 mm Cu and higher for HVT over 2 mm Cu than the spectral calculations. The low values may be due to an underestimate of the contribution of the saturated scatter to the depth doses by the above mentioned method. This is indicated by the fact that if the contribution of the saturated scatter is taken from a table for short focus skin distance the calculated integral dose will be greater than for a greater focus skin distance. The integral doses estimated from eq. 3 are greater for a short focus skin distance because the field was small and thus the contribution of scattered radiation is greater for greater depths (JOHANSSON et coll.). When the scatter contribution is already saturated one may instead expect the reverse for a short focus skin distance, as in this case the intensity of the border radiation decreases according to the inverse square law. Increased reflection and inhomogeneities in the field also play a role (Fig. 13).

As the energy albedo has been calculated for a semi infinite phantom the reflection will be overestimated to a greater extent for thinner water slabs. This results in an underestimate of the spectral calculations of the integral doses, especially at large HVT. This may be the reason for the lower values of the integral doses calculated from the spectra for the higher HVI. It must be admitted however that the calculations of the transmission are so inaccurate that nothing definite may be said concerning these small deviations.

To compare the calculations with those of other authors the results published by SCARIA (1960), KELLER (1956), REINSMAN (1962), and ZIEGLER (1961) have been added in Fig. 13 to the results from Figs. 12. SCARIA uses the saturated scatter method and his results are approximately identical with the results based on the Meredith Neary method. The calculations of KELLER give

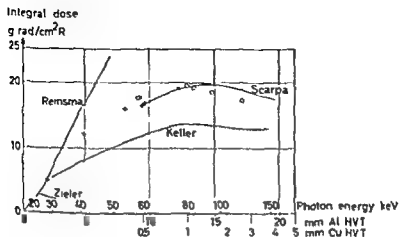


Fig. 13 Integral doses per cm<sup>2</sup> and R calculated by different authors are added to fig. 12

appreciably lower results whereas REMSMA simply assumes that all of the incident energy is absorbed. He neglects backscatter and transmission and assumes that the HVT well describes the radiation quality. Neglecting the spectral differences for radiation with the same HVT involves a faulty estimation of the dose-saving effect of the filtration of a roentgen tube. In his measurements of integral doses, properly incident energy, in roentgen diagnostic examinations he uses a roentgen tube with an inherent filtration equivalent to 2 mm Al. He compares measured integral doses without and with an added filter composed of 0.2 mm Cu + 1 mm Al and does not observe any decrease of the integral doses in spite of the fact that the skin doses decrease by a factor of 4 for the heavier filter. The decrease of the integral dose (incident energy) produced by the filter is concealed as he underestimates the incident energy more for the unfiltered radiation than for the filtered. This is evident from Fig. 8 where the HVT varies between 1.5 and 1 mm Al for unfiltered radiation and between 4 and 9 mm Al for filtered radiation.

ZIELER (1961) also calculates integral dose from exposure measurements and energy absorption coefficients for air. Like REMSMA he chooses for this heterogeneous and low energy radiation an average absorption coefficient taken from monoenergetic radiation with the same HVT. On the other hand he estimates the energy loss due to scattering and transmission in various phantoms. He uses the energy flux density (spherical intensity) instead of the energy current density (plane intensity) in his estimate of the reflected and transmitted energies (BEWLEY et coll. 1959; IANO et coll. 1959; WILKINSON 1961). The reflected and transmitted energy will then be overestimated by up to a factor 2 which means a grave underestimate of the integral dose.

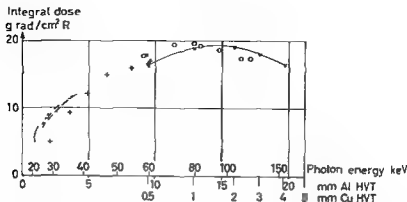


Fig 12 Combination of figs 11 and 10. The integral doses calculated from depth doses and spectral measurements can be compared

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## AUTORADIOGRAPHIC LOCALIZATION OF STRONTIUM 85 IN OSTEOSARCOMAS

by

I. E. APPELGREN, A. NILSSON and S. ULLBERG

The only isotopes that have been used up to now in autoradiographic distribution studies with radiostrontium seem to be  $^{86}\text{Sr}$  and  $^{90}\text{Sr}$ . These are both exclusively beta emitters with the relatively high maximum energies of 0.55 and 1.5 MeV respectively.

Strontium 85 has been used mainly in experiments connected with external measurements. Its 0.513 MeV gamma radiation has then been registered by scintillation detectors.  $^{85}\text{Sr}$  also emits short range extranuclear electrons (main energy about 11.5 keV) which theoretically are very suitable for high resolution autoradiography.

The present authors in earlier investigations with transplanted bone forming osteosarcomas (3, 4) found a more rapid strontium turnover in tumours than in normal bone. The autoradiograms revealed a very rapid uptake of  $^{85}\text{Sr}$  in the actively growing tumour tissue soon after injection followed later by a rapid decrease in concentration.

In the present investigation the early uptake of radiostrontium in transplanted osteosarcomas has been studied in more detail by means of autoradiography. An improved autoradiographic resolution was obtained, mainly

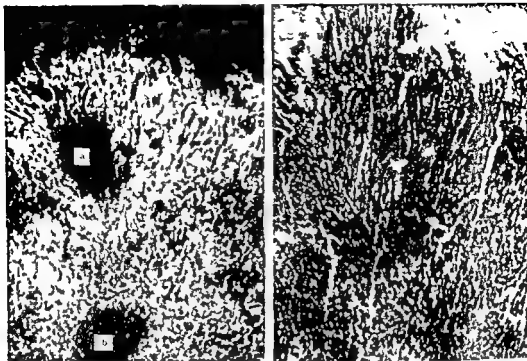


FIG. 1. *Left* Autoradiogram of part of a transplanted osteosarcoma 4 hours after injection of  $^{85}\text{Sr}$ . White areas correspond to high radiostrontium uptake. High uptake is evident in bone trabeculae. Two areas (a) and (b) show very low  $^{85}\text{Sr}$  uptake. *Right* Section corresponding to the autoradiogram stained with von Kossa's silver. Heavy mineralization is generally related to  $^{85}\text{Sr}$  uptake. The trabeculae in areas corresponding to the  $^{85}\text{Sr}$  free parts (a) and (b) in the autoradiogram are slightly more slender than in neighbouring parts of the tumour.  $\times 40$ .

because of the more favourable radiation properties of  $^{85}\text{Sr}$  as compared with  $^{90}\text{Sr}$ .

**Methods**  $^{85}\text{Sr}$  nitrate in  $\text{HNO}_3$  solution, was purchased from Oak Ridge Tennessee USA. The specific activity was 8 718 mCi/g.

Inbred CBA mice were used as experimental animals. Small pieces (about  $2 \times 2 \times 2$  mm) of  $^{85}\text{Sr}$  induced osteosarcomas were transplanted to the subcutaneous dorsal region of the neck of other CBA mice. The tumours had been used for transplantation in several generations of animals and had lost their original content of  $^{85}\text{Sr}$ , in two months they had reached a diameter of 2.5 to 3 cm.

Strontium 85 (80  $\mu\text{Ci}$ ) was injected intraperitoneally after development of the transplanted tumour and autoradiograms were obtained of sagittal whole body sections through the mice which were killed four hours later by immersion in a dry ice and acetone mixture.

Section thicknesses varied from 5 to 20  $\mu$ . The autoradiographic exposure



Fig 2 Transplanted osteosarcoma with highly mineralized tumour bone (lower part of view) and a peripheral narrow zone of soft tumour tissue (upper part of view) where trabecular bone has not yet been formed van Gieson  $\times 100$

was made by apposition against Ilford G 5 nuclear plates (emulsion thickness  $4\ \mu$ ), or films of the Schumann type (Kodak SWR) with the silver bromide layer confined to the surface of the emulsion. The exposure time was 16 days. The autoradiographic method has been described earlier (5, 6). The sections were stained by the von Kossa method after the autoradiographic exposure. Sections for histologic examination  $5\ \mu$  in thickness were also stained with haematoxylin eosin azure cosinate (Lillie) or according to van Gieson.

### Results

The most peripheral part of the tumour consists of a narrow zone of cellular soft tissue without detectable mineralization (Figs 1 and 2); there is no noticeable  $^{85}\text{Sr}$  uptake in this area (Fig. 1). The next zone contains well developed mineralized trabeculae (Fig. 3) with highly active osteoblasts (Fig. 4) and mostly intact blood vessels. This area shows the most active uptake of  $^{85}\text{Sr}$  in the autoradiograms.

The lines of high uptake of  $^{85}\text{Sr}$  in the autoradiograms correspond well with the bone trabeculae in the von Kossa stained sections (Fig. 1). A number of small islands ( $10\ \mu$  to  $1\ \text{mm}$  in diameter) are seen in the zone of generally intact obviously first growing tumour tissue and these in the autoradiograms present evidence of little or no uptake of  $^{85}\text{Sr}$ . The uptake of  $^{85}\text{Sr}$  gradually rises to match that of the surroundings at the periphery of these dead islands (Fig. 1). The degree of mineralization occasionally appears in the corresponding areas of the von Kossa stained sections. Similar islands with varying degrees of cellular degeneration from a hardly noticeable granulation of the osteoblasts to complete necrosis of the tumour bone may be found in the histologic sections (Fig. 5).





Fig 3 Transplanted tumour. Highly mineralized necrotic area at upper right corner. Gieson  $\times 100$ .

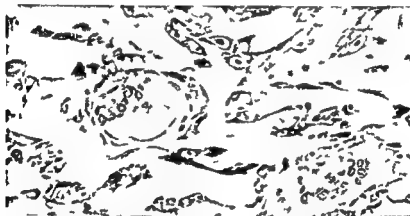


Fig 4 Area from a transplanted tumour, with blood vessels, well developed tumour bone and highly active osteoblasts. Azure eosinate  $\times 400$ .

### Discussion

The use of  $^{90}\text{Sr}$  in autoradiography has led to a striking improvement in resolution compared with earlier experiences with  $^{89}\text{Sr}$ . This is probably mainly due to the contribution of the short range extranuclear electrons emitted by  $^{90}\text{Sr}$  (1, 2).

The monoenergetic electrons of  $^{90}\text{Sr}$  have predominant lines at about 11.5 keV, in the neighbourhood of the energy of tritium (max. energy 18 keV). The range for such electrons is  $2.2\ \mu$  in water. The electron radiation may be expected to dominate in causing blackening of the photographic emulsion in autoradiography with thin sections and emulsions, in work with sections

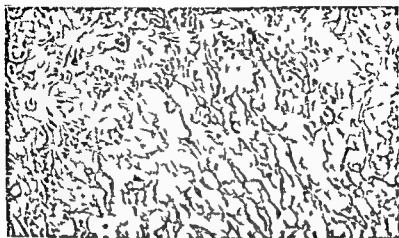


Fig 5 Transplanted osteosarcoma with necrosis of the tumour bone. Empty lacunae and debris between the narrow trabeculae (van Gieson  $\times 100$ )

considerably thicker than the range of the electrons; however, it can be expected that the electromagnetic (roentgen) radiation of  $^{85}\text{Sr}$  (energy 13.3 keV) significantly contributes to the blackening of the emulsion. If the absorption in water is considered, the roentgen radiation of  $^{85}\text{Sr}$  (half thickness about 3.3 mm) is less advantageous for autoradiographic resolution than the beta radiation of  $^{90}\text{Sr}$  (range about 1.8 mm or half thickness about 0.25 mm); the situation will be the converse, however, if the absorption in the photographic emulsion is considered. With an emulsion consisting of 50 per cent silver bromide and 50 per cent gelatine (v/v), the half thickness of the  $^{90}\text{Sr}$  betas is about  $70\ \mu$ , while that of the 13.3 keV roentgen radiation of  $^{85}\text{Sr}$  is only about  $50\ \mu$ .

Attention has not been paid in the above calculation to the fact that the autoradiographic resolution with  $^{90}\text{Sr}$  is impaired by the influence from the yttrium 90 daughter.

Concerning the uptake of radiostrontium in the tissues, the results agree with the previous observation of a very high early uptake of radiostrontium in tumour as compared with normal bone. The distribution within the tumour tissue, however, was highly irregular with marked differences in uptake both between the various zones from the periphery and inwards and within the zones.

The appearance of strontium 85 free areas in zones of rapid tumour growth may probably be related to blood vessel damage. Autoradiography appears to be a sensitive method for discovering metabolic changes in such areas before any histologic signs can be detected.

### Acknowledgement

The authors are indebted to S. Forberg, Division of Nuclear Chemistry, Royal Institute of Technology, Stockholm, for valuable advice.

### SUMMARY

Improved resolution has been obtained with strontium 85 as compared with strontium 90 in autoradiographic investigations of the distribution of radiostrontium in bone forming osteosarcomas. A much higher uptake of radiostrontium was found in tumour than in normal bone, the distribution being highly irregular and related to the varying degrees of mineralization and degenerative changes.

### ZUSAMMENFASSUNG

Strontium 85 zeigte ein besseres Auflösungsvermögen als Strontium 90 in autoradiographischen Untersuchungen über die Verteilung von radioaktivem Strontium in knochenbildenden Osteosarkomen. Es ergab sich, dass beträchtlich mehr radioaktives Strontium im Tumor als im normalen Knochengewebe aufgespeichert wurde; die Verteilung des Strontium erfolgte recht unregelmässig, je nach dem Mass der Knochenbildung oder der Entartungsprozesse.

### RÉSUMÉ

Dans l'étude autoradiographique de la distribution du radiostrontium dans les ostéosarcomes ostéogéniques, le strontium 85 donne une meilleure résolution que le strontium 90. On trouve une fixation de radiostrontium beaucoup plus élevée dans la tumeur que dans les os normaux; sa distribution est très irrégulière et liée aux variations de la minéralisation et aux modifications dégénératives.

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## RADIOPROTECTIVE EFFECTS OF S PHOSPHORYLATED THIOLS

by

STIG ÅKERFELDT

It was recently reported by HANSEN & SORBO (1961) as a result of a search for new radioprotective substances at this institute that one of the S phosphorylated thiols earlier synthesized by ÅKERFELDT (1959) namely cysteamine S phosphate is a potent radioprotective agent when given to mice. This fact has stimulated the synthesis of a series of related compounds (ÅKERFELDT 1962) and a preliminary investigation of their properties as potential anti radiation drugs is reported in this paper.

**Methods** Male mice of an inbred CBA strain 10 to 12 weeks old and weighing  $22 \pm 2$  g were used in this investigation. Total body irradiation was delivered from a roentgen generator operated at 260 kV and 10 mA with 4 mm Al and 0.5 mm Cu filters. Furthermore an irregular copper filter (average thickness 0.1 mm) was inserted to counteract differences in radiation intensity in different parts of the radiation field. The animals were kept in plastic cages during irradiation. The FID was 40 cm and the dose rate  $74 \text{ min}^{-1}$ . The total roentgen dose given was 1092 r which corresponded to  $LD_{50}$ . The  $LD_{50}$  for this mice strain used was 718 r.

The compounds to be investigated were dissolved in saline adjusted to pH 7 and 0.3 ml of the solution injected intraperitoneally into 30 mice 15 min before irradiation. The amount of compound injected into each animal corresponded roughly to 1/10th estimation of  $LD_{50}$ .

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Table 1

*Acute toxicities and radioprotective effects of S phosphorylated thiols*

No	Compound	LD <sub>50</sub> mmole per kg bodyweight	Dose mmole per kg bodyweight	30-day survival
1	NH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> SH	4.0	1.75	93-100
2	NH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> SPO <sub>3</sub> HNa*	5.2	2.2	95
3	CH <sub>3</sub> \NCH <sub>2</sub> CH <sub>2</sub> SPO <sub>3</sub> Na <sub>2</sub>	> 0.5	0.5	0
4	(CH <sub>3</sub> ) <sub>2</sub> \NCH <sub>2</sub> CH <sub>2</sub> SPO <sub>3</sub> Na <sub>2</sub>	3.0	0.5	0
5	(CH <sub>3</sub> ) <sub>2</sub> \NCH <sub>2</sub> CH <sub>2</sub> SPO <sub>3</sub> Na	0.2	0.08	0
6	(1-C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> \NCH <sub>2</sub> CH <sub>2</sub> SPO <sub>3</sub> Na <sub>2</sub>	0.7	0.5	0
7	C-\NCH <sub>2</sub> CH <sub>2</sub> SPO <sub>3</sub> (NH <sub>4</sub> ) <sub>0.2</sub> Li <sub>0.8</sub>	1.7	1.4	97
	NH <sub>2</sub>		0.7	53
8	NH CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> SPO <sub>3</sub> HLi	> 1.0	1.0	4
	NH			
9	C-\N(CH <sub>3</sub> ) <sub>2</sub> SPO <sub>3</sub> (NH <sub>4</sub> ) <sub>0.8</sub> Li <sub>0.2</sub>	1.6	1.0	80
	NH <sub>2</sub>		0.5	13
10	(CH <sub>3</sub> ) <sub>2</sub> \NCH <sub>2</sub> CH(CH <sub>3</sub> )SPO <sub>3</sub> Li <sub>2</sub>	1.8	1.5	81
			0.75	13
11	NH <sub>2</sub> COCH <sub>2</sub> SPO <sub>3</sub> Li <sub>2</sub>	> 1.0	1.0	0
12	HOCH <sub>2</sub> CH <sub>2</sub> SPO <sub>3</sub> Li <sub>2</sub>	> 1.0	1.0	0
13	HOCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> SPO <sub>3</sub> Na <sub>2</sub>	1.0	0.5	0
14	CH <sub>3</sub> CH <sub>2</sub> SPO <sub>3</sub> Li <sub>2</sub>	> 1.0	1.0	0
15	Li PO <sub>3</sub> SCH <sub>2</sub> CH(OH)CH <sub>2</sub> SPO <sub>3</sub> Li	0.2	0.13	0
16	Li PO <sub>3</sub> SCH <sub>2</sub> CH(SPO <sub>3</sub> Li <sub>2</sub> )CH <sub>2</sub> OH	0.3	0.25	0

\* Calculated from data by HANSEN &amp; SORBO (1961)

and LD<sub>50</sub> was obtained after intraperitoneal injection of the substances (dissolved in 0.3 ml saline) into 10 to 30 mice. Thirty control mice given 0.3 ml of saline and 30 mice injected with 0.3 ml of saline containing cysteamine corresponding to 1.75 millimoles per kg body weight were used in each experiment.

Cysteamine S-phosphate + cysteamine in tissues after intraperitoneal injection of cysteamine S-phosphate was determined in the following way. The tissue was homogenized in its double volume of 10% cold trichloro-acetic acid. After centrifugation a sample of the clear supernatant was heated for 2 min at 100° and cysteamine in the solution was determined colorimetrically according to GRUNERT & PHILLIPS (1951).

The chromatographic methods used for the identification of urinary excretion products of injected cysteamine S-phosphate have been reported elsewhere (ÅKERFELDT 1959).

### Radioprotective effects of S-phosphorylated thiols

The results are presented in Table 1. It is evident that of the new compounds tested three have good radioprotective properties, namely 1 guanidinoethanethiol 2 phosphate (compound No. 7), 3 guanidinopropionethiol S phosphate (compound No. 9) and 2 dimethylamino 1 methylethanethiol S phosphate (compound No. 10). These three substances are good radioprotectors at concentrations below those necessary for a protective effect with cysteamine or cysteamine S phosphate but they are more toxic. Reduction of the dose considerably decreases the effectiveness of the compounds Nos 9 and 10 but does not affect the protective action of compound No. 7 to the same extent. A concentration intermediary to those investigated for compound No. 7 may therefore be sufficient for maximal protectivity of this substance.

Table 1 clearly shows that substitution of R in compounds containing an unbranched carbon chain  $R(CH_2)_nSPO^{2-}$  (where  $n = 2$  or  $3$ ) for hydrogen, alkylated amino groups or hydroxyl groups produces compounds that are completely ineffective as radioprotectors at the dose levels tested.

Compound No. 15 has the same spacing between the sulfur atoms as lipoic acid and compound No. 16 is diphosphorylated British Anti Lewisite (BAL). Both are relatively toxic and have no radioprotective effects in the concentrations tested. For protective effect, the substituent (R) must include an unsubstituted  $NH_2$  group such as the guanidino or amino group. It is noteworthy that the  $NH_2$  group of the amide No. 11 is devoid of protective activity. This is probably due to the tautomeric properties of the amido group.

The radioprotective properties of compound No. 10 are surprising. This is the first instance in which a substance containing an alkylated amino group has been shown to be a potent radioprotector. Since the analogue with an unbranched carbon chain (No. 4) is ineffective the action of compound No. 10 must be associated with the presence of an  $\alpha$  methyl group.

*Mode of action.* S phosphorylated thiols are easily hydrolyzed enzymically by a number of tissues of the animal body. The products formed are ortho phosphate and a thiol (ÅKERFELDT 1960, 1962). It would therefore appear that the radioprotective effect of S phosphorylated thiols is at least partly due to the enzymic formation of thiols from these compounds. This conclusion is also supported by the following facts:

1. Variation of the structure of the substituent and of the length of the carbon chain has the same influence on the radioprotectivity of S phosphorylated thiols as it has on that of the corresponding thiols (LANGENDORFF & KOCH 1956, SHAPIRA et coll. 1957, and DOHERTY et coll. 1957).

2. The guanidino derivatives Nos 7 and 9 are effective at the same dose levels as are the corresponding thiols (SHAPIRA et coll. 1957). Compounds Nos 7 and 9 and the corresponding thiols are not effective when given after irradiation. This was the case also with compound No. 10.

Table 2

*Concentration of cysteamine + cysteamine S phosphat (CASP) in various organs of mice 0.5 and 1 hour after intraperitoneal injection of 0.11 mmole cysteamine S phosphate in 0.3 ml saline*

Organ	$\mu$ mole SH/g tissue control animal*	$\mu$ mole SH/g tissue CASP animal		Difference between CASP and control animal $\mu$ mole SH/g tissue	
		0.5 hour	1 hour	0.5 hour	1 hour
Liver	7.05	11.1	10.1	4.05	3.05
Spleen	1.23	3.83	3.12	2.60	1.89
Kidney	4.82	14.4	8.60	9.58	3.78

\* Calculated as cysteamine

Table 3

*Concentration of cysteamine + cysteamine S phosphate (CASP) in various organs of rats 0.5 and 1.5 hours after intraperitoneal injection of 0.34 mmole cysteamine S phosphate in 0.6 ml saline*

Organ	$\mu$ mole SH/g tissue control animal*	$\mu$ mole SH/g tissue CASP animal		Difference between CASP and control animal $\mu$ mole SH/g tissue	
		0.5 hour	1.5 hours	0.5 hours	1.5 hours
Liver	5.30	5.94	7.00	0.64	1.70
Kidney	5.01	5.51	5.30	0.50	0.29
Spleen	2.86	3.56	3.14	0.70	0.28
Marrow	0.76	1.12	1.78	0.36	1.02

\* Calculated as cysteamine

*Distribution of intraperitoneally injected cysteamine S phosphate in various organs of the mouse and rat* It was mentioned that cysteamine S phosphate and other S phosphorylated thiols are rapidly hydrolyzed by enzymes present in various organs of mammals. Intraperitoneally injected cysteamine S phosphate will therefore be recovered in various tissues both as cysteamine and as unchanged cysteamine S phosphate. (In addition, small amounts of other metabolites may possibly be present.) The method chosen to investigate the concentrations of the injected radioprotector in the tissues was such that it measured both cysteamine and unchanged cysteamine S phosphate. The deproteinized acid tissue homogenate was therefore hydrolyzed at 100° for a few minutes, a procedure that gives a quantitative yield of cysteamine from any cysteamine S phosphate present (ÅKERFELDT 1962). This technique is superior to the one using <sup>35</sup>S labelled compounds, since it measures only the amount of radio protector present, it does not measure the amounts of possible metabolites (which do not contain the thiol group).

Organs of mice and rats that had received 0.11 to 0.34 millimoles cysteamine S phosphate intraperitoneally were analyzed 0.5, 1 and 1.5 hours

after the injection. Representative results are presented in Tables 2 and 3 and show that the radioprotector rapidly increases the amount of available thiol groups in all tissues studied. These results are in agreement with earlier studies performed on cysteamine, e.g. by SORBO (1962), who also demonstrated that the increased thiol concentration in liver and spleen could not be attributed only to the cysteamine present in the blood of these tissues.

*Urinary excretion products of cysteamine S phosphate.* Paper chromatographic analysis of urine collected from rats that had received intraperitoneal injection of cysteamine S phosphate was performed (a) on untreated urine (b) after coupling of the excreted thiols to 6 chloromercuri 2 nitrophenol (ÅKERFELDT 1959), and (c) after iodine oxidation of the excreted thiols.

The results showed that only traces of cysteamine S phosphate remained. Small amounts of cysteamine were found but by far the largest portion of the cysteamine S phosphate injected had been hydrolyzed to cysteamine which was the only detectable thiol present. Hypotaurine and taurine were possibly present in trace amounts.

The main urinary excretion products are thus cysteamine and ortho phosphate.

### Acknowledgements

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### SUMMARY

Fourteen different S phosphorylated thiols have been investigated as to their radioprotective properties in mice. The distribution of intraperitoneally injected cysteamine S phosphate in certain organs of rats and mice and the urinary excretion products of cysteamine S phosphate were also examined.

### ZUSAMMENFASSUNG

Vierzehn verschieden gegen radio-aktive Körper S phosphorylierte Thiole in bestimmten Abbauprodukten

S phosphorylierte Thiole wurden an Mäusen auf ihren Schutzwert geprüft. Die Verteilung von intraperitoneal injiziertem Cysteaminsphosphat in bestimmten Organen von Ratten und Mäusen sowie die renale Ausscheidung Cysteaminsphosphates wurden ebenfalls untersucht.

### RÉSUMÉ

Les propriétés radioprotectrices de quatorze thiols S phosphorylés différents ont été étudiées sur la souris. L'auteur a aussi examiné la distribution de certains organes de rats et de souris du S phosphate de cystéamine injecté dans le péritoine et les produits d'excrétion urinaire du S phosphate de cystéamine.



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## PROTECTIVE EFFECT OF CYSTEAMINE AT FRACTIONATED IRRADIATION

### I Lethality up to 30 days after last irradiation

by

ARNE NELSON, OLA HERTZBERG and INCA BRITT HENRICSSON

A considerable amount of information is accumulating on the protective effects of numerous chemical compounds in acute injuries measured as lethality caused by single whole body irradiation (reviewed by ELDJARN & PHIL (1960), and others). Few attempts have however been made to investigate the effect of protective substances at fractional irradiation up to accumulated lethal doses or at continuous long term irradiation.

PATT et coll (1953) investigated the protective effect of cysteine on mice by using a split exposure technique. The interval between successive radiation fractions did not, however exceed 5 min. The two fractions varied from 100 to 700 r and the amount of cysteine injected was proportional to the radiation dose. PATT concluded from his results that irradiation prior to cysteine administration does not influence the protection against subsequent exposure and that the lethal potential of small dosages of radiation cannot be reversed by cysteine under these conditions.

RUGH & CLUGSTON (1954) could not observe any protective effect of cysteine

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amine on mice given 100 r per day. The protected mice died after an average accumulated dose of 1 230 r, the corresponding value for the controls being 1 440 r. LANGENDORFF & CATSCH (1956) gave two doses of 175 to 500 r with 24 hour intervals and found a protective effect of cysteamine, which, however, was less than that with single doses. Later LANGENDORFF *et coll.* (1959) tested the effect of serotonin. They gave three fraction doses of 505 to 1 100 r with 30 day intervals and 750 to 1 050 r with 15 day intervals and observed a good protective effect. NOBLE *et coll.* (1960) gave ten daily doses of 50 to 200 r to mice and noticed a protective effect with AET. DOULL *et coll.* (1960) in a similar investigation observed a significant reduction in the 30 day mortality with serotonin and dimethyldithiocarbamide acid, but no effect with cysteamine.

The few studies on the protective effects obtained have resulted in equivocal results due to the rather limited range of fraction doses, intervals and accumulated doses. It is likely that an investigation with a wider range would give valuable information concerning the mechanisms of protection and of recovery, and in answer to the question whether the chemical protection is due to a dose reduction effect or to an enhanced recovery, might perhaps be obtained.

The present investigation is an attempt to elucidate some of these problems.

### Material and Methods

*Animals.* In all experiments only male mice of an inbred CBA strain were used. Their age was 60 to 70 days at the first irradiation.

*Irradiation conditions.* The roentgen apparatus was operated at 260 kV and 10 mA, filter 0.5 mm Cu, inherent filtration 4 mm Al, dose rate 84 r/min, distance between the roentgen tube and the object approximately 40 cm.

The animals were irradiated in groups of ten in a plastic 'wheel' and were then placed together in a cage. Because of the growth of the animals during the experimental period, single animals were suffocated in the radiation wheel. The area of the breathing holes in the wheels was therefore increased to give the animals ample air supply, this possibly influenced the radiosensitivity. This change was made between two series of experiments in August 1961, but one group (160 r, 7 days) was carried through at the changed conditions.

The irradiation schedule giving fractionated doses, accumulated doses, and intervals, is presented in Tables 1 to 7.

Groups of animals consisting of about 60 mice were exposed under the same irradiation conditions. Half the number received an intraperitoneal injection of 3 mg cysteamine 15 min before the irradiation.

*Controls.* In several of the untreated control groups, each consisting of 50 mice, no deaths occurred during the observation time, which in some cases was extended to 11 months.

Table 1

Mortality after fraction dose 80 r — time interval 1 day (numbers in italics not tested)

Series started	Accumulated dose (AED) (r)	Number of animals		Distribution of deaths during observation time (days)						Survival at end of observation	Mortality
		At beginning of irradiation	At end of irradiation	1-5	6-10	11-15	16-20	21-25	26-30		
13.2.62	640	30	30							30	
	640	30	27					1		26	1
	960	30	30	1						29	
	960	30	29							29	33
	1280	30	30	2	2	2				24	20.0
	1280	30	23	2	1					20	33.3
	1600	30	27	3	8	4	2			4	86.6
	1600	30	17	2	1				1	13	57.7
	1920	30	15	13	1	1				0	100.0
	1920	30	13	2	3	3				5	83.2
28.8.62	640	20	20							20	0
	800	20	20							20	0
	960	20	20			1				19	5.0
	1120	20	19							19	5.0
	1280	20	20	4	1					15	25.0
	1440	20	17	3	2					12	40.0
	1600	20	11	5						6	70.0
	1760	20	8	4	3					1	95.0

The toxicity of cysteamine was tested in some non irradiated groups. Of 50 mice receiving cysteamine every day for 24 days, 48 survived and out of 49 mice injected once a week for more than 40 weeks 46 survived.

A mathematical model (see below) based on the results of the first series in 1960—1961 was designed and used for an extended examination in 1961—1962. Complementary experiments were carried out during the autumn of 1962 in order to obtain further confirmation of the applicability of the mathematical model.

The mortality in the early series was observed up to only 30 days after the last irradiation. The observation in the later series was extended to the life span of the animals. Only the 30 day mortality is reported in this paper, however.

### Results

The results of the experiments are presented in Tables 1 to 7, they are reported upon in groups defined by a certain fraction dose at a given interval.

Table 2

Mortality after fraction dose 160 r — time interval 1 day (numbers in italics indicate protected groups)

Series started	Accumulated exposure dose (M.D.) (r)	Number of animals		Distribution of deaths during observation time (days)						Survivals at end of observation time	Mortality
		At beginning of irradiation	At end of irradiation	1-5	6-10	11-15	16-20	21-25	26-30		
17 I 62	480	30	30							30	0
	<i>480</i>	30	30							<i>30</i>	<i>0</i>
	800	30	30		3	3				24	20 0
	<i>800</i>	30	30		<i>1</i>					<i>29</i>	<i>3 3</i>
	1 120	30	30		24	4				2	93 2
	<i>1 120</i>	30	30		<i>13</i>	<i>3</i>				<i>14</i>	<i>53 3</i>
	1 440	30	30	6	24					0	100 0
	<i>1 440</i>	30	29	6	23					0	<i>100 0</i>
	1 760	30	30	26	4					0	100 0
	<i>1 760</i>	30	29	19	3					0	<i>100 0</i>
28 B 67	480	20	20							20	0
	800	20	20							20	0
	1 120	20	20		15	2				6	70 0
	1 440	20	20	5	13	2				0	100 0

1 Fraction dose 80 r, interval 1 day (Table 1) No conclusions can be drawn regarding any protective effect against radiation from the series in which cystermine has been tested. It is, however, apparent that the protected animals which survived the treatment period showed a lower mortality during the observation time than those that were unprotected. The accumulative toxic effect of the substance must also be taken into consideration. It was often noted during this experimental series that the death of animals occurred in close connection with injection of cystermine or with irradiation. This phenomenon will form the subject of a special investigation.

2 Fraction dose 80 r, interval 3 days. In accordance with the mathematical model, no acute death occurred in this series. The results will therefore be reported in a paper on chronic effects.

3 Fraction dose 160 r, interval 1 day (Table 2) In spite of the daily repeated irradiations, only a few unprotected animals could not tolerate higher accumulated doses, but the number of survivals was significantly higher compared with the number unprotected. Because of the relatively low number of cystermine injections no accumulated toxic effect was observed.

4 Fraction dose 160 r, interval 3 days (Table 3) All animals survived after 960 r but some unprotected mice died after 1 280 r. The mortality increased con-

Table 3

Mortality after fraction dose 160 r — time interval 3 days (numbers in italics indicate protected groups)

Series started	Accumulated exposure dose (AED) (r)	Number of animals		Distribution of deaths during observation time (days)						Survivals at end of observation time	Mortality
		At beginning of irradiation	At end of irradiation	1-5	6-10	11-15	16-20	21-25	26-30		
71160	960	30	30							30	0
	960	30	30							30	0
	1280	30	30		1	2				27	10.0
	1280	30	29							29	3.3
	1600	30	29	1	3	7	4	1		12	60.0
	1600	30	30							30	0
	1920	30	27	17	4	1				5	83.7
	1920	30	35							0	0
27861	1600	30	29	9	7	2				11	63.4
	1600	30	29	2	2	3	2		1	19	36.7
	1920	29	23	13	6	3				1	96.5
	1920	30	29	3	6	4			1	15	50.0
	2240	30	6	5	1					0	100.0
	2240	30	24	1	4	1				18	49.0
	2560	30	2	1	1					0	100.0
	2560	30	12	4	3					5	83.3
	2880	30	0							0	100.0
	2880	30	3	2	1					0	100.0
	3200	30	0							0	100.0
	3200	30	1	1						0	100.0
	3200	30	0							0	100.0
	3200	30	2	1						1	96.7
28862	960	20	20							20	0
	1280	20	20							20	0
	1600	20	20				1			19	5.0
	1920	20	15	8	3	2				2	90.0
	2240	20	13	6			2		1	4	80.0

siderably after 1600 r and after 2240 r all the animals died. The protective effect of cysteamine is apparent: the protected mice did not begin to die until after 1600 r and some survived even after 2560 r.

5. Fraction dose 160 r interval 7 days (Table 4). All the irradiated unprotected mice survived an accumulated dose of 2240 r. After 3200 r about 50% of the animals survived, but in the dose range of 3840 r to 4800 r only a few mice survived. All animals died after 5760 r. A significant increase in the number

Table 4

Mortality after fraction dose 160 r — time interval 7 days (numbers in italics indicate protected groups)

Series started	Accumulated exposure dose (AED) (r)	Number of animals		Distribution of deaths during observation time (days)						Survivals at end of observation time	Mortality
		At beginning of irradiation	At end of irradiation	1-5	6-10	11-15	16-20	21-25	26-30		
19860	1280	30	30							30	0
	<i>1280</i>	30	30							30	0
	1600	30	30							30	0
	<i>1600</i>	30	30							30	0
	1920	30	30							30	0
	<i>1920</i>	30	30							30	0
	2240	35	35							35	0
	<i>2240</i>	35	35							35	0
17561	2880	28	23		1		2	2		18	35.7
	<i>2880</i>	27	25							25	44
	3200	29	27	1	6	1	2	1	1	15	48.3
	<i>3200</i>	29	21	2		1	2	1		15	49.3
	3520	29	15	1		2				12	58.6
	<i>3520</i>	29	28					1		27	1.9
	3840	28	5		1	1		1	1	1	96.5
	<i>3840</i>	28	14		2			1	1	10	61.3
	4160	28	8	4	2	1				1	96.5
	<i>4160</i>	23	5					1		4	81.0
	4480	27	4				1		1	3	97.5
	<i>4480</i>	30	17	1	1			2		13	57.7
	4800	28	2		1					1	96.5
	<i>4800</i>	29	14		3		1			8	7.3
	5760*	28	1	1						0	100.0
	<i>5920**</i>	27	1	1						0	100.0

\* This group should have been irradiated 40 times. The last mouse died on the day following the 37th irradiation.

\*\* This group should have been irradiated 40 times. The last mouse died on the 5th day following the 37th irradiation.

of survivors was observed among the protected groups in the dose range of between 3520 r and 4800 r, in comparison with the unprotected groups. All the mice were dead after 5920 r, however.

6. Fraction dose 320 r, interval 1 day (Table 5). All unprotected animals survived an accumulated dose of 640 r, but already at 960 r the majority had died, and all were dead after 1280 r. A few protected mice died at 960 r, at 1280 r some survived, and at 1600 r all died.

Table 5

Mortality after fraction dose 320 r — time interval 1 day (numbers in italics indicate protected groups)

Series started	Accumulated exposure dose (AED) (r)	Number of animals		Distribution of deaths during observation time (days)						Survivals at end of observation time	Mortality
		At beginning of irradiation	At end of irradiation	1-5	6-10	11-15	16-20	21-25	26-30		
1366)	640	30	30							30	0
	640	30	30		1					29	3.3
	960	30	30	4	7	9		1		9	70.0
	960	30	29	1						28	6.7
	1280	30	30	1	28	1				0	100.0
	1280	30	29		12	9	1			7	76.8
	1600	35	32	5	27					0	100.0
	1600	35	24	3	20	1				0	100.0

7 Fraction dose 320 r interval 3 days (Table 6) Some unprotected mice died already at an accumulated dose of 960 r and the mortality was 100 % at doses higher than 1280 r. Some of the protected animals died after 1280 r but some survived at 1920 r indicating a good protection also in this case.

8 Fraction dose 320 r, interval 7 days (Table 7) A few deaths are recorded among the irradiated animals only at accumulated doses of 1280 r and 1600 r but at 1920 and 2240 r only a few survived. A very low mortality in the protected animals is however, evident in this dose range and at 3200 r some survivors still remain. The protective effect of cysteamine in this group is obvious.

### Mathematical model and Statistical analysis

According to the general opinion the recovery rate decreases in the time intervals between irradiations. This implies that the recovery rate during the first 24 hr after an irradiation should be greater than the recovery rate during the following 24 hr. Furthermore the recovery rate is considered to be dependent on a previous irradiation (see BARR 1961; BACHTER 1958; STORER 1961).

Systematic deviations indicating that a simpler model would be evident when these concepts were applied to the present data. A mathematical model as therefore designed on the assumption that the recovery rate was independent of an previous dose and independent of the time interval between irradiations. The recovery rate per day was assumed to be the same for each animal. The effective dose received by an animal is then

$$\text{ERD} = \text{AED} - R \cdot T$$

where AED is the accumulated exposure dose, R the recovery rate in r/day and T is the number of recovery days in the time period between the first and last irradiation (Fig. 1). If  $R \cdot T \geq \text{AED}$  ERD = defined as 0.



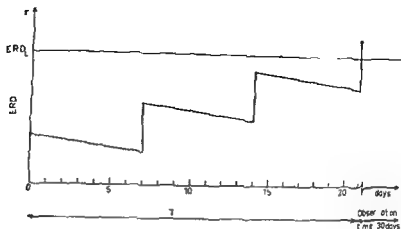


Fig. 1 ERD in  $r$  as a function of recovery time ( $T$ ) for an animal whose  $ERDL$  is exceeded in the last irradiation

Table 6

Mortality after fraction dose 320 r — time interval 3 days (numbers in italics indicate protected groups)

Series started	Accumulated exposure dose (AED) (r)	Number of animals		Distribution of deaths during observation time (days)						Survivals at end of observation time	Mortality
		At beginning of irradiation	At end of irradiation	1-5	6-10	11-15	16-20	21-25	26-30		
5760	960	30	30		6	3				21	30.0
	960	30	30							30	0.0
	1180	30	30	13	13	2	1		1	0	100.0
	1280	30	30		2	2	1			25	16.7
	1600	30	30	33	7					0	100.0
	1600	30	30	7	9	3	1			10	66.7
	1920	35	19	19						0	100.0
	1970	34	33	13	13	3				4	88.3
7461	960	30	30		2	5				23	23.3
	960	30	30							30	0.0
	1280	30	30		24	2	3			1	96.6
	1280	30	30		3		1	2	1	23	23.3
	1600	30	28	27	1					0	100.0
	1600	30	30	12	10	1			1	6	80.0
	1920	30	9	9						0	100.0
	1970	20	11	5	7					0	100.0
	2240	30	3	3						0	100.0
	2240	20	10	5	4	1				0	100.0
	2560	30	0							0	100.0
	2560	29	2	2						0	100.0

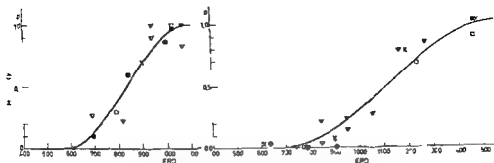


Fig 2 Mortality as a function of ERD (series I) a) irradiated only b) irradiated and protected.

- 160 r 3 days started 7.11.1960
- × 320 r 1 day » 13.6.1960
- 320 r 3 days » 5.7.1960
- 320 r 3 days » 7.4.1961
- ▽ 320 r 7 days » 22.9.1960
- ▼ 320 r 7 days » 7.2.1961

Table 7

Mortality after fraction dose 320 r — time interval 7 days (numbers in italics indicate protected groups)

Series started	Accumulated exposure dose (AED) (r)	Number of animals		Distribution of deaths during observation time (days)						Survivals at end of observation on time	Mortality %
		At beginning of irradiation	At end of irradiation	1-5	6-10	11-15	16-20	21-25	26-30		
22.9.60	1280	30	10			4	2	2		22	26.7
	1280	30	30							30	0.0
	1600	30	10	1		3			1	23	23.4
	1600	30	30							30	0.0
	1920	30	27	10	10	4				3	90.0
	1920	30	29							29	3.3
	2240	35	26	13	5	1	1			6	82.8
	2240	35	35		2	2	1			30	14.3
7.2.61	1920	30	15	14	1					0	100.0
	1920	28	27	1			2	1	1	22	21.4
	2240	30	1	1						0	100.0
	2240	30	27	4						23	23.4
	2560	29	29							0	100.0
	2560	30	24	2						27	26.7
	2880	30	30							0	100.0
	2880	30	10	1		1			1	7	76.6
	3200	30	30							0	100.0
	3200	30	6			1				5	83.4

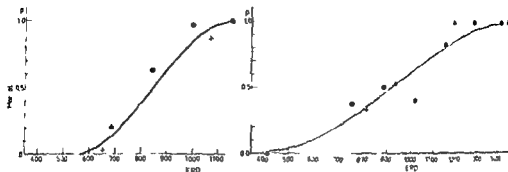


Fig 3 Mortality as a function of I RD (series II) a) irradiated only b) irradiated and pre-treated

+ 80 r 1 day started 1 14?  
 Δ 160 r 1 day 1 1 16?  
 ● 160 r 3 days " 1 1 11

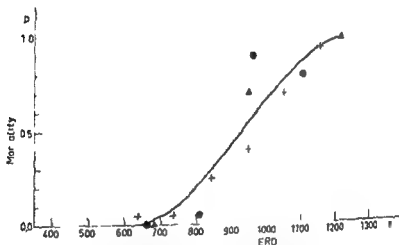


Fig 4 Mortality as a function of I RD (series III) irradiated only

+ 80 r 1 day started 28 8 14 2  
 Δ 160 r 1 day 28 8 14 2  
 ● 160 r 3 days 28 8 14 2

I RD is thus the accumulated dose corrected for such recovery as has occurred at a specific time (T)

If during the irradiation period the dose received by an animal exceeds a certain value (FRD), death occurs according to the model before the end of the observation time  $t =$  within 30 days after the last irradiation. It appears from Fig. 1 that if FRD is not exceeded at the last irradiation the animal will survive.

The relationship between mortality and dose in our animal material may be expressed as a sine square distribution and this has therefore been assumed in our model for the distribution of FRD. The relation between mortality and I RD will form an S shaped curve which will only differ slightly from the normal distribution. When the sine square distribution is applied the observed mortality rate  $p$  is transformed according to

$$y = 2 \arcsin \sqrt{p} \text{ in which case} \\ y = a + b (I RD) \text{ (a and b are constants)}$$

After substitution of ERD

$$y = a + b (\text{AED} - R \cdot T) = a + b (\text{AED}) - c \cdot T \text{ where } c = b \cdot R$$

The variable  $y$  can accept values between 0 and  $\tau$

By means of regression analysis  $a$ ,  $b$  and  $c$  can be estimated in which case an estimation of

$R = \frac{c}{b}$  can be obtained

The statistical analysis gave the following equations for the five regression planes

$$\text{Ser I Ir} \quad y = -3.39 + 0.005979 (\text{AED}) - 0.1651 T \quad R = 28$$

$$\text{Ser I Ir} + P \quad y = -2.39 + 0.003536 (\text{AED}) - 0.1086 T \quad R = 31$$

$$\text{Ser II Ir} \quad y = -2.80 + 0.005148 (\text{AED}) - 0.1435 T \quad R = 20$$

$$\text{Ser II Ir} + P \quad y = -1.06 + 0.002876 (\text{AED}) - 0.0901 T \quad R = 31$$

$$\text{Ser III Ir} \quad y = -3.15 + 0.005098 (\text{AED}) - 0.1496 T \quad R = 29$$

(Ir = irradiated P = protected)

Series I includes experimental groups started not later than April 4th 1961 series II was started between August 22nd 1961 and February 13th 1962 while series III was started on 28th of August 1961

Thus  $y$  is the expected value of  $y$  according to the model From  $y$  the expected mortality can be calculated which for  $0 \leq \hat{y} \leq \tau$   $0 \leq p \leq 1$

$y < 0$  is regarded as  $p = 0$  and  $y > \tau$  as  $p = 1$

The estimations of ERD can be obtained for each group of animals from AED  $T$  and the estimation of  $R$

The curves in Figs 2, 3 and 4 give the relation between  $p$  and ERD The observed mortality rates are marked in the figures

The curves for Ir + P are extended over a greater range of ERD than the curves for Ir only  $e.g.$  the standard deviation of  $ERD_L$  is greater for the protected than for the unprotected animals The mean square deviation of the observed values around the function that indicates the relationship between dose and mortality should not be significantly greater than the theoretical variance determined by the binomial distribution The mean square deviation around the lines in Figs 2, 3 and 4 is however significantly greater than the theoretical variance This might depend on those age differences that arise due to the long duration of the experiment even if the animals were of the same age at its inauguration In addition it should be pointed out that the various groups in series I and II were investigated at different times

The most important control investigation of the validity of the model is an observation of systematic deviations  $e.g.$  if points based on the same experimental conditions in Figs 2, 3 and 4 tend to show a systematic shift in relation to the curves It is evident from Fig 2a that some points show a deviation from the curve which is great in comparison with the expected deviation defined by the binomial distribution although a systematic deviation is not observed in any group Neither in Fig 2b where protection has been added can any systematic deviation be observed

A systematic deviation is noted in Figs 3 and 4 which could indicate a higher recovery rate after a low dose  $e.g.$  the points of the 80 r and 1 day group show a lower mortality than might be expected There is however no reason to conclude from the result that the recovery rate for the 160 r and 1 day group should be greater than the recovery rate for the 160 r and 3 day group

## Conclusions

The mathematical model was designed as a means of providing a statistical analysis of the acute lethal effect of fractionated irradiation In the case of sufficiently low fraction dose or long enough interval it is within 30 days after

the last irradiation, no acute mortality is observed. When the duration of the experimental period is very extended, chronic effects will influence the results and a systematic deviation from the model is introduced, e.g. in the 160 r and 7 day groups. Such a systematic deviation has, however, not been observed within 90 days from the first irradiation in the present study. No conclusion can be drawn regarding the validity of the model at shorter times since no experiment has been carried out with intervals shorter than 24 hours between the fraction doses.

The good agreement between the recovery rates of the irradiated as well as of the irradiated protected groups both in series I and II, in spite of the fact that the experiments were carried out at different times, is of great interest. Somewhat higher recovery rates have certainly been observed among the animal groups that received cysteamine but the difference must be regarded as insignificant.

The protective influence of cysteamine is apparent and the recovery rates are practically the same in the protected and unprotected groups which further supports the opinion that the results produced by cysteamine are initial, i.e. dose reduction effects.

### Acknowledgement

The authors are indebted to C. Ronnback, S. Jäger, I. Andersson and R. von Knorring for their excellent technical assistance.

### SUMMARY

Groups of mice were exposed to fraction doses at various time intervals in order to investigate the protective effect of cysteamine at sublethal levels of irradiation. Half the number of animals were given cysteamine before each irradiation. A simple mathematical model which fitted the results regarding the short term lethal effects was used. Cysteamine appears to act by producing a dose reduction effect and not an enhancement of the recovery.

### ZUSAMMENFASSUNG

Gruppen von Mäusen wurden fraktionell bei verschiedenen Zeitabständen bestrahlt um den Schutzeffekt von Cysteamin von nicht tödlichen Strahlendosen zu beurteilen. Die Hälfte der Tiere erhielten Cysteamin vor jeder Bestrahlung. Ein einfaches mathematisches Modell wurde benutzt das die Resultate der rasch tödlichen Effekte darstellte. Cysteamin scheint mehr eine Reduktion der Strahlendose zu bewirken als die Erholung von einer Strahlendose zu begünstigen.

### RESUMÉ

Des groupes de souris ont été exposés à des doses fractionnées à intervalles de temps variés pour étudier l'effet protecteur de la cystéamine pour des taux d'irradiation subléthaux. La moitié de ces animaux ont reçu de la cystéamine avant chaque irradiation. Les auteurs se sont servis d'un modèle mathématique simple qui concordait avec les résultats concernant l'effet léthal à court terme. La cystéamine semble agir par un effet de réduction de dose et non en favorisant la guérison.

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## STRAHLENSCHUTZ UND DEKONTAMINATION IN ISOTOPENLABORATORIEN

von

ULRICH O. SCHANZE

Die ständig weitergehende Anwendung von offenen radioaktiven Isotopen in allen Naturwissenschaften in Medizin und Technik erfordert eine umfangreiche Beachtung der Schädigungsmöglichkeiten durch radioaktives Material. Wenn auch die grundsätzlichen Vorsichtsmaßnahmen und Hilfsmittel zur Verhinderung einer Kontamination bekannt sein durften und in vielen Veröffentlichungen niedergelegt sind, erscheint es dennoch ratsam, auf dies bezüglich spezielle Probleme des Strahlenschutzes hier einzugehen. Dazu gehören eine Anleitung zum Vorgehen nach Unfällen mit radioaktiver Substanz, nebst Hinweisen zur Dekontamination, Empfehlungen für die Behandlung radioaktiv kontaminierter Wäsche und eine Übersicht über Arten und Verwendung von Strahlungsmonitoren im Radioisotopen Labor.

*Verhalten bei Unfällen mit offener radioaktiver Substanz und Hinweise zur Dekontamination.* Selbst beim vorsichtigen Arbeiten sind gelegentliche, meist nur kleine Unfälle nicht zu vermeiden. Radioaktives Material, welches dabei auf die Haut oder die Kleider kommt, kann leicht inkorporiert werden wie auf Tischen.

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Bei der Redaktion am 13. November 1962 eingegangen



Bild 1 Strahlenschutzwagen einsatzfähig gepackt

Fußboden, Händen usw. gelangte Radioisotope auch bald über Kleider und Hände den Weg in den Körper finden können.

Bei einem Zwischenfall mit offener radioaktiver Substanz kann es sich um Aktivitäten von einigen  $\mu\text{C}$  als auch um mC Mengen handeln, welche durch unglückliche Umstände und/oder durch Ungeschicklichkeit verschüttet wurden. Dann ist schnelles Handeln geboten, um zu verhindern, daß sich radioaktive Flüssigkeit durch die Kleider saugt oder pulverisierte radioaktive Substanz verstaubt und so auf die Haut oder in die Atemwege gelangt und daß die kontaminierte Area weiter ausgebreitet wird. Dann muß möglichst sofort mit der Reinigung und der Dekontamination begonnen werden. Auch ist darauf zu achten, daß die betreffende Person, die nun einmal eingetretene Verseuchung nicht weiter verschleppt, was etwa beim übereilten Aufsuchen des Waschraumes oder auch aus anderen Gründen der Fall sein kann.

Es hat sich als zweckmäßig und sehr vorteilhaft erwiesen, daß alle zur Dekontaminierung und zur Überwachung derselben benötigten Dinge nicht erst jeweilig zusammengetragen werden müssen, sondern an einer Stelle stets greifbar sind. Der hier beschriebene Strahlenschutzwagen (Bild 1) enthält alle diese Dinge übersichtlich geordnet (MALLARD 1956). Er soll im Laboratoriums trakt jedoch nicht in einem Heißlabor, Meßraum oder Isotopenlager selbst an gut zugänglicher Stelle stehen — etwa im Flur — und kann im Bedarfsfalle durch ein oder zwei Personen, die nicht in die Kontamination verwickelt sind, zum Unfallort gebracht werden. Der Wagen selbst ist ähnlich den in der ärztlichen Praxis verwendeten fahrbaren Instrumententischen aus Stahlrohrkonstruktion mit zwei Etagen. Er soll nicht zu kleine Räder besitzen. Die Bestückung des Strahlenschutzwagens kann in drei Gruppen eingeteilt werden, nämlich



## Monitoren (Strahlenschutzmeßgeräte)

## Schutzbekleidung und Schutzstoffe

## Materialien und Hilfsmittel zur Dekontamination

welche im folgenden einzeln beschrieben und mit Hinweisen versehen sind

## Monitoren

- 1 Strahlenmonitor mit Ionisationskammer empfindlich für  $\beta$  und  $\gamma$  Strahlen geeignet in mßb. batteriebetriebenen Zur Kontrolle des Strahlungsspiegels als Dosisleistung sehr praktisch in Pistolenform
- 2 Strahlenmonitor mit Zählrohr empfindlich für  $\beta$  und  $\gamma$  Strahlen wenn erforderlich auch für  $\alpha$  Strahlen mit sehr dünnem Fenster oder Szintillationssonde netz oder batterie betrieben geeignet in Impulse/Minute Zur Kontrolle des Strahlungsspiegels und von Kontaminationen als Impulsrate Auswechselbare Zählrohr wünschenswert genügend lange Zählrohr und Netzkabel erforderlich
- 3 Zwei Stück Taschendosimeter Meßbereich 0,2 r höchstens 1 r Zur persönlichen Dosiskontrolle während des Unfalles als Extrameßung Diese Dosimeter müssen sich immer im geladenen Zustand befinden

## Schutzbekleidung und Schutzstoffe

- 4 Zwei Stück Schutzkleider (Haltform) oder weit übergreifend Schürzen lang aus Plastik in zwei verschiedenen Größen
- 5 Zwei Paar Gummihandschuhe normal in zwei verschiedenen Größen fertig mit Talkum zum Hineinschlupfen versehen
- 6 Zwei Paar Gummihandschuhe dick mit kurzen Stulpen in zwei verschiedenen Größen fertig mit Talkum zum Hineinschlupfen versehen
- 7 Zwei Paar Gummistiefel in zwei verschiedenen Größen
- 8 Zwei Stück lange Greifzangen mit zwei verschiedenen Griffen etwa Harwell Typ oder gleichwertige andere Typen am besten mit Pistolengriff
- 9 Zwei Stück längere Tiegelzangen vernickelt oder Edelstahl in einem Standglas
- 10 Behälter für radioaktive Abfälle mit leicht zu öffnendem Deckel und austauschbarem Einsatz aus Kunststoff (Wird außen am Strahlenschutzwagen angehängt)
- 11 Drei Stück flache Schalen verschiedener Größen zum Ablegen kontaminierter Gegenstände u. d. Werkzeuge
- 12 Zwei Stück PVC Decken etwa 1 x 2 m zum vorläufigen Abdecken kontaminierter Gebiete oder ähnlichen Verwendungszwecken
- 13 Zwei Stück Gasmasken siehe Text

## Materialien und Hilfsmittel zur Dekontamination

- 14 Zellstoff in Bogen zum Abwischen
- 15 Saugfähiges Filterpapier in Bogen zum ersten Aufnehmen verseuchter Objekte (Luftböden)
- 16 Kunststoff Abwischlappen und Pinsel zum Bedecken von radioaktiv verseuchten Oberflächen
- 17 Kreide zum Bezeichnen von Kontaminationslinien
- 18 Drei bis fünf Liter flüssige Seife zur Dekontamination
- 19 1 Liter 1% Kaliumpermanganatlösung zur Hautentseuchung
- 20 1 bis 2 Liter Kaliumbissulfatlösung 5% zum Gebrauch nach Benutzung von Kaliumpermanganatlösung
- 21 Kunststoffbeutel mit Reißverschluß zum Aufbewahren kontaminierter Kleidungsstücke
- 22 Je ein bis zwei Liter Treiblösungen der jeweils verwendeten Radionuklide (für ein medizinisches Isotopenlaboratorium etwa Jod- und Phosphortreiblösung) Siehe Text

- 23 100 ml Natriumperchloratlösung (12 g auf 90 ml) in graduierter Flaschen Nur notwendig wenn mit Radiojod gearbeitet wird Siehe Text
- 24 Ein liter Natriumthiosulfatlösung gesättigt Siehe Text
- 25 Langstielliger Mop zum Aufschieben nicht mit Holzstiel (Mit 2 Schellen außen am Strahlenschutzwagen angeklemt)
- 26 Kunststoffeimer zum Aufwischen und Eintauchen des Mops (Hangt in einem Ring außen am Strahlenschutzwagen unter dem Mop)

Diese Aufstellung ist sowohl ausführlich durchdacht als auch in jahrelangem Einsatz praktisch erprobt, erhebt jedoch keinen Anspruch auf Vollständigkeit. Deshalb sind Abänderungen für spezielle Zwecke nicht nur möglich sondern oftmals sogar nötig. Auch kann die hier beschriebene Grundausstattung beliebig erweitert werden (So empfiehlt z. B. MALLARD (1956) noch je einen Satz der wichtigsten Frauen- und Männerkleidungsstücke).

Bei einem Unfall mit radioaktiven Substanzen müssen vor allem die betroffenen und helfenden Personen Ruhe und Besonnenheit bewahren, und gerade bei solchen Zwischenfällen zeigt sich die Wichtigkeit einer guten Ausbildung über den Umgang und die Wirkung mit und von Radioisotopen.

Der Strahlenschutzwagen wird zum Unfallort gebracht jedoch nur so nahe an das Verseuchungszentrum heran, daß der Wagen selbst keiner Kontamination ausgesetzt ist. Der oder die Helfenden legen Schutzkleider, Gummihandschuhe (Normalausführung die dicken mit kurzen Stulpen dienen vor allem als zusätzlicher Handschutz bei mitunter notwendigem Hineingreifen in radioaktives Material), und Gummieverschuhe an. dazu Taschendosimeter. Letztere dienen zur gesonderten Ermittlung der Personendosis während aller Arbeiten am Unfallort. Anschließend gilt das Hauptaugenmerk der von der Kontamination betroffenen Person welche an eine Stelle niedrigen Strahlungsspiegels gebracht werden soll jedoch ohne dabei Radioaktivität zu verschleppen. Der Helfende benutzt dabei den batteriebetriebenen Ionisationskammer Monitor zur Feststellung der jeweils herrschenden Dosisleistung. Es ist zur Vereinfachung und zur Beschleunigung der Hilfsarbeiten günstig wenn zwei Personen hierzu zur Verfügung stehen. Eine übernimmt dann die mehr aktiven Handlungen im direkten Kontakt mit der Kontamination die andere die mehr passiven Tätigkeiten wie Handhabung der Monitore und Zureichen.

Wenn offensichtlich ist daß die Haut auch kontaminiert oder gar das Gesicht mit radioaktiver Substanz in Berührung kam dann soll unverzüglich an der nächsten Waschanleitung die betroffene Stelle mit viel Wasser abgewaschen werden. Kleider die radioaktiv getränkt oder bestäubt wurden sind sofort abzulegen und in dem Kunststoffbeutel für die Dekontamination aufzubewahren. Auch hierbei spielt die richtige Anwendung der Monitore eine große Rolle. Betroffene Hautstellen sind nach dem Abwaschen mit Wasser sofort mit in flüssige Seife getauchten Zellstofflappen die zweckmäßigerweise in einer Tiegelfange gehalten werden zu behandeln und wieder mit Wasser abzuwaschen. Reicht dies nach kurzer Zeit nicht aus so sind Zellstofflappen in

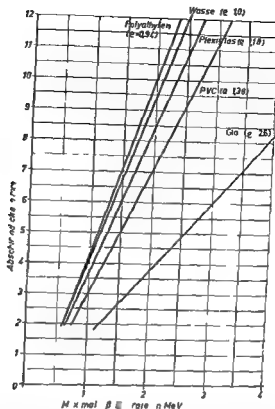


Bild 2 Dicke verschiedener Stoffe die zur völligen Abschirmung der  $\beta$  Strahlen nötig ist in Abhängigkeit von der maximalen Betaenergie — Abschirmdicken für andere als in dem Bild angegebene Stoffe können abgeschätzt werden da sie etwa der Dichte des Stoffes umgekehrt proportional sind

Trägerlösung (Trägerlösungen sind inaktive Formen der verwendeten radioaktiven Verbindungen) getaucht zu benutzen. Letztere Methode ist meistens erfolgreich, wenn aber doch noch eine Hautkontamination nachweisbar ist (Zählrohrmonitor), muß etwa 1 Minute mit Kaliumpermanganatlösung gewaschen werden und danach mit der Natriumbisulfitlösung, welche die hautschädigende Wirkung des Kaliumpermanganats kompensiert. Auch bietet die pharmazeutisch-chemische Industrie hautdekontaminierende Waschmittel an, die auch verwendet werden können.

Übertriebenes Reiben der betroffenen Hautstellen ist unbedingt zu vermeiden, um nicht durch Zerkratzen oder Aufrauen der Haut eine Ingestion radioaktiven Materials ins Blut zu ermöglichen. Jedenfalls sollte zunächst eine Reduktion der  $\beta$  und  $\gamma$  Impulsrate über den betroffenen Stellen von unter 1000 Imp/mm erreicht werden (Endfensterzählrohr hierzu benutzen, und vergleiche Tabelle 2 für die endgültigen Werte).

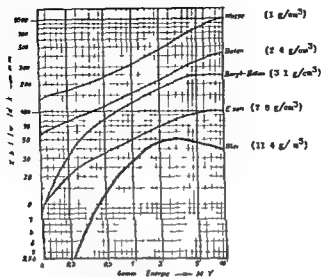


Abb 3 Zehntelwertschichten verschiedener Strahlenschutzabsorber

Es muß darauf hingewiesen werden daß größere Hautverseuchungen besonders an empfindlichen Stellen, wie Gesicht und Leib wohl niemals beim Tragen der richtigen Schutzkleidung und Beachten der nötigen Vorsichtsmaßregeln (siehe Literaturverzeichnis) auftreten.

Handelt es sich bei dem verschütteten Radioisotop um  $^{131}\text{J}$  so ist es empfehlenswert der betreffenden Person eine Dosis von 200 mg Natriumperchlorat pro 6 Stunden zu verabreichen. Dies sind 15 ml aus dem graduerten Vorratsfläschchen des Strahlenschutzwagens. Dadurch wird die Inkorporation des Radiojods in der Schilddrüse blockiert und seine Ausscheidung aus dem Körper beschleunigt.

Spritzer radioaktiver Flüssigkeiten an nicht absorbierender Schutzkleidung können mit Zellstoff abgewischt und danach wie üblich dekontaminiert werden (Zählrohrmonitor gebrauchen vergleiche hierzu Tabellen 2 und 3 auch Ref 6).

Sind die beschriebenen Hilfeleistungen an der betroffenen Person durchgeführt wendet man sich den Reinigungs und Dekontaminierungsarbeiten in dem verseuchten Labor zu. Unter Verwendung von Ferngreifzangen und langen Tiegelzangen (besonders bei Gammastrahlern) beziehungsweise mit den dicken Gummihandschuhen (bei Betastrahlern) wird hierzu zunächst saugfähiges Päckpapier dann Zellstoff genommen und nach Gebrauch in den Abfallbehälter des Strahlenschutzwagens geworfen. Gleichzeitig sind dabei

Tabelle 1

*Halbwertszeiten, Halbwertschichten und Dosiskonstanten verschiedener gammastrahlender Radionuklide (nach QUIMBY)*

Isotop	HWZ	HWs cm Blei	Dosiskonstante r pro mC h bei 1 cm
Natrium 24	15 <sup>h</sup>	1.5	18.4
Kalium 42	12.5 <sup>h</sup>	1.2	1.50
Chrom 51	28.8 <sup>d</sup>	0.2	0.4
Mangan 52	5.8 <sup>d</sup>	1.0	19.0
Eisen 59	45.0 <sup>d</sup>	1.1	6.55
Kobalt 60	5.2	1.2	13.5
Kupfer 64	12.8 <sup>h</sup>	0.4	1.1
Zink 65	245.0 <sup>d</sup>	1.0	2.7
Brom 82	35.7 <sup>h</sup>	1.0	15.1
Jod 131	8.0 <sup>d</sup>	0.3	2.18
Caesium 137	30.0	0.5	3.2
Gold 198	2.7 <sup>d</sup>	0.3	2.35

Scherben und ähnliches zu entfernen. Bei schwachen  $\alpha$  oder  $\beta$  Strahlern können als Abfallbehälter auch große Papiertüten verwendet werden (Ref. 5).

Zweckmäßigerweise wird die mit einem Monitor festgestellte verseuchte Area mit Kreide bezeichnet, wobei es manchmal ratsam ist, auch Dosismesswerte mit anzuschreiben, um die Reinigungs- und Dekontaminierungsarbeiten innerhalb der benachbarten Stellen zu erleichtern. Dadurch wird auch bei spielsweise verhindert, daß eine zu große Fläche aufgewischt und damit womöglich noch kontaminiert wird, weil sonst oftmals auf einmal die ganze Oberfläche naß ist und man nicht mehr weiß, wo das eigentliche Verseuchungszentrum ist.

Konzentrationen stärkerer Betaaktivität, etwa mit Gefäßbruchstücken zusammengetragene radioaktive Substanz, läßt sich — wenn erforderlich — zeigt der Ionisationskammermonitor an — leicht durch Kunststoffplatten völlig abschirmen (Bild 2). Besonders empfiehlt sich Plexiglas und durchsichtiges PVC in einer Dicke von etwa 10 mm. Hingegen werden solcherart Anhäufungen gammastrahlender Isotope am besten hinter einigen schnell aufgestellten Bleiziegeln zusammengetragen. Dabei ist möglichst großer Abstand zu halten, die langen Greifzangen zu benutzen und die Anzeige des Ionisationskammer-Monitors zu beachten.

Es erscheint noch zweckmäßig, an dieser Stelle auch auf die Halbwertschichten und die Dosiskonstanten der Gammastrahler hinzuweisen, deren Benutzung die Bestimmung von Abschirmungen resp. Dosisleistungen erleichtert (Tabelle 1). Bei den hier interessierenden Strahlenschutz Zwecken ist es allerdings günstiger, statt der Halbwertschicht die 'Zehntelwertschicht' (Bild 3) zu

Tabelle 2

Empfehlungen für maximal zulässige äußere Verunreinigungen in Laboratorien für Radioisotope (nach GUSSEI)

Verunreinigung (Zerfälle/min auf 150 cm<sup>2</sup> Fläche)

	Für Alpha Strahler		Für Beta Strahler	
	Vor Dekontamination	Nach Dekontamination	Vor Dekontamination	Nach Dekontamination
Hande	75	ohne	5 000	ohne
Wasche oder Handtuch	75	ohne	5 000	ohne
Laborkleidung aus Baumwolle	500	100	25 000	5 000
Schutzkleidung aus Plastik	500	200	25 000	10 000
Schutzhandschuhe Außenseite	500	100	25 000	5 000
Überschuhe Außenseite	500	200	25 000	5 000
Arbeitstische Gegenstände	500	200	25 000	5 000

benutzen deren Großen sofort wegen der höheren Schwachung anwendbar sind

Vor dem Fortsetzen der nächsten Reinigungsarbeiten müssen die erwähnten größeren radioaktiven Abfallmengen in geeigneten Behältnissen entfernt werden. Zum Transportieren und Aufbewahren radioaktiver Abfälle haben sich Behälter mit herausnehmbaren Kunststoffeinsätzen bewährt, die gegen  $\alpha$ -Strahler mit Blei und gegen  $\beta$ -Strahler mit PVC abgeschirmt sind.

Nach dem Aufnehmen der verschütteten radioaktiven Substanz beginnt die eigentliche Dekontamination, die unter Verwendung beider Monitoren sehr sorgfältig vorzunehmen ist. Auch in größerer Entfernung vom Verseuchungszentrum ist zu messen. Eine wirksame Methode zur Dekontamination von Fußboden, Tischen usw., ist flüssige Seife oder ein anderes starkes Reinigungsmittel über die betroffene Fläche zu gießen und dann mit einem langstieligen Mop aufzuwischen. Dieser Vorgang ist im Bedarfsfalle zu wiederholen. Wenn erforderlich, kann auch noch mit Tragerlösung nachbehandelt werden. Sollte auch diese Methode nicht zum Ziele führen, schlägt MALLARD vor, einen abziehbaren Kunststofflack über die verseuchten Stellen zu streichen, was ein Freiwerden radioaktiver Dämpfe oder Staubes verhindert. Die betreffenden Teile müssen dann später ausgewechselt und wie fester Abfall behandelt werden.

Leider geben die von der I C R P herausgegebenen Empfehlungen keine Angaben über zulässige Oberflächenkontamination. In den Tabellen 2 u. 3 sind deshalb einige von anderer Seite angegebene Werte gebracht, um die maximalen äußeren Verunreinigungen zahlenmäßig darzustellen und die Handhabung der Monitoren zu erleichtern. Dabei gilt Tabelle 3 (nach DUNSTER

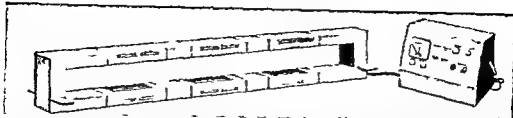


Bild 4 Wasche Prüfungsmonitor (mit freil. Genehmigung des Herstellers Technical Assoc. Burbank California) Links Messrahmen rechts Anzeigegerät mit noch einer flexiblen Handsonde (Endfenster zahlrohr) Messbereich 0—2 000 Imp./min Ansprechzeit 2 bis 4 sec Empfindlichkeit um 0,15  $\mu\text{C}/\beta$

1955) für ausgedehnte Flächenkontamination, also bereits für schwierigere Fälle, siehe Anmerkung daselbst. Gleichzeitig sei an dieser Stelle auf die von der I A E O herausgegebenen Sicherheitsrichtlinien (Ref. 6) hingewiesen. Maximale Konzentrationen reiner Gammastrahler lassen sich unter Beachtung der Toleranzdosis recht gut mit dem Ionisationskammer Monitor finden.

Die bei der Bestückung des Strahlenschutzswagens erwähnten Gasmasken werden im Falle einer Verschüttung radioaktiven Pulvers (Staubschutz) oder radioaktiven Dampf erzeugender Flüssigkeit (Gasschutz) gebraucht (MAL LARD). Bei Radiojoddampf soll das Baumwollfilter der Gasmaske vorher mit Natriumthiosulfatlösung getränkt werden und wenigstens etwas wieder getrocknet sein, denn dann werden etwa 80 % des durchgehenden Radiojod dampfes absorbiert. In einem richtig eingerichteten Laboratorium für Radioisotope (SCHANZE 1957) werden über alle Arbeiten mit solchen Stoffen mindestens in einem Abzug (der bei einem Zwischenfall einfach geschlossen wird) oder besser in einer 'glove box' (SCHANZE 1959 GRAUL 1958) ausgeführt.

Ein bei allen diesen Betrachtungen wichtiger Faktor ist die physikalische Halbwertszeit. So genügt bei kurzlebigen Radioisotopen wie etwa  $^{131}\text{I}$ ,  $^{24}\text{Na}$  die Aufbewahrung kontaminierter Gegenstände in geeigneten Behältnissen über einige Halbwertszeiten, um die gewünschte Aktivitätsreduktion durch Abklingen herbeizuführen. Auch bei der Lagerung radioaktiver Abfälle ist dieses von Bedeutung.

Zur Dekontamination von Gerät hat sich folgende Mischung bewährt: 3 Volumenteile 10 % ige  $\text{HNO}_3$  werden mit 1 Volumenteil  $\text{C}_2\text{H}_5\text{OH}$  vermischt und etwas 'Pril' (Netzmittel) zugesetzt. Natürlich gelten die im Zusammenhang mit dem Vorgehen nach Unfällen mit radioaktiver Substanz gemachten Dekontaminierungshinweise auch für allgemeine, also nicht unfallgebundene Reinigungsarbeiten. Den Detergentien kommt jedenfalls bei der gesamten Dekontamination besondere Bedeutung zu. Speziell bei hartnäckigen oder kritischen Fällen (etwa nach in Bleikammern zerbrochenen Becherglasröhren) wird

Tabelle 3

*Empfehlungen für maximal zulässige Flächenkontamination (nach DUNSTER)*

$10^{-5}$ Ci/cm <sup>2</sup>	für die Alphastrahler Po210 Ra226 Ac227 Pu239
$10^{-4}$ $\mu$ Ci/cm <sup>2</sup>	für alle anderen Alpha strahler
$4 \times 10^{-4}$ Ci/cm <sup>2</sup>	für alle Betastrahler

(An begrenzten Flächen bis 100 cm<sup>2</sup> pro m<sup>2</sup> können die angegebenen Werte um den Faktor 10 vergrößert werden. Dieses gilt jedoch nicht für Kleidung oder für Gegenstände die irgendetwie mit dem Munde in Berührung kommen können.)

sowohl Titandioxyd mit verdünnter HCL als auch Siliziumchlorid zur Geratedekontamination empfohlen. Die Kombination der beiden Mittel soll besonders wirksam sein. Auch sei an dieser Stelle auf die von der I A E O herausgegebenen Ausführungen (Ref. 6) hingewiesen.

Da eine Dekontaminierung von Geräten in Isotopenlabors wiederholt und regelmäßig erforderlich ist, empfiehlt es sich, diese Arbeiten immer an bestimmter Stelle (Spule) vorzunehmen. In vielen Fällen ist hierzu auch eine besondere glove box geeignet. Für größere Isotopenlabors wird am besten eine sogenannte Dekontaminierungskammer dafür bereitgestellt.

Um den Strahlenschutzwagen und seine Einrichtung jederzeit wieder einsatzbereit zu haben, ist es erforderlich, nach Inanspruchnahme verbrauchte Bestandteile und Lösungen zu ergänzen, Schalen, Abfallbehälter, Zangen usw. zu entleeren, zu reinigen, zu dekontaminieren und zum neuen Gebrauch wieder herzurichten. Einzelne Bestandteile sollten dem Strahlenschutzwagen nicht entnommen werden, um ihn immer einsatzbereit und komplett zu haben.

*Behandlung und Umgang mit radioaktiver Wasche.* Es erscheint erforderlich, zu diesem bisher nur wenig behandeltem Thema einiges zu sagen, weil dieses für die Laboratoriumskleidung und für das Bettzeug vieler radiologischer Kliniken von Bedeutung ist und auch eine Dekontaminierungsfrage darstellt.

Eine Schwierigkeit taucht zunächst auf, nämlich zu entscheiden, ob und welche Waschestücke in die normale Wascherei gegeben werden können und welche besonders dekontaminiert beziehungsweise extra gewaschen werden müssen. Radioaktiv gewordene Wasche kann nach DUNSTER immer dann mit der gewöhnlichen Schmutzwäsche zusammen gewaschen werden, wenn fest steht, daß einmal die Kontamination durch den normalen Waschprozeß sicher beseitigt wird und zum anderen die Aktivitäten ziemlich niedrig sind. Auch die Gefährlichkeit (Radioaktivität) des kontaminierenden Radioisotopes (Ref. 6 u. SCHÄNZE 1957) und die Art seiner chemischen Verbindung



spielen dabei eine Rolle. So können z. B.  $\beta$ -Verunreinigungen schwer entfernt sein, wenn sich unlösliche Phosphate bilden.

Sorgfalt und Kenntnis erfordert auch das Prüfen der Waschestücke vor dem Waschen mit dem Monitor (Endfensterzählrohr benutzen), sowie das Handhaben und Sortieren. Dabei sind immer Gummihandschuhe, bei Gammastrahlern noch lange Tiegelszangen zu benutzen. Bei schweren Gamma-Verunreinigungen, z. B. Unfallwasche, kann Bleigummischutz für Hände und Körper — wie im Röntgenwesen gebräuchlich — trotz der hohen Gammaenergien diskutabel sein. Die Möglichkeit einer äußeren Strahleneinwirkung und ein Inhalationsrisiko sind wohl meistens vorhanden. Zweckmäßig sind zum Sortieren mit PVC bedeckte Tische, deren Rand hochgezogen ist. Auch können bei starker Beta-Verunreinigung z. B. Unfallwasche Schutzschilde aus transparentem Kunststoff nützlich werden.

Unkompliziert wird nach DUNSTER das ganze Problem, wenn die meisten Waschestücke mit nicht mehr als  $10^{-2} \mu\text{C}/\text{cm}^2$  an Betastrahlern kontaminiert sind, auch wenn einige Stücke das zehnfache dieses genannten Wertes aufweisen, denn die Dekontamination von  $\beta$ -Aktivitäten dieser Größenordnung in der normalen Wascherei bringt keine Komplikationen mit sich. Dennoch wird es sich auch bei diesen geringen Aktivitäten überall dort lohnen, wo relativ viel solche Wasche anfällt, eine besondere separate Waschanlage in einem eigenen Raum einzurichten.

Eine solche 'aktive' Wascherei wird am besten dem Laboratoriumstrahl oder der Bettenstation angeschlossen und für größere Aktivitäten ausgelegt. Zu ihrer Haupteinrichtung gehören Waschmaschine (gute Haushalts- oder Industriewaschmaschine), Schleuder (auch in Kombination möglich), sowie je ein besonderer Tisch für die Handhabung kontaminierter und gewaschener Wäsche. Die Benutzung einer separaten Waschanlage gilt grundsätzlich für alle größeren Isotopenlabors und Kliniken, in denen offene Radionuklide in größerem Umfang appliziert werden. Überhaupt muß Wasche, die höhere Aktivitäten als oben genannt respektive Alpha- oder Gammastrahler in sich aufgenommen hat, extra gewaschen werden.

Zu berücksichtigen ist weiterhin, daß das Waschen kontaminierter Wäsche einen sekundären radioaktiven Flüssigkeitsstrom aus der Waschlauge und dem Spülwasser erzeugt, der deshalb der Anlage zur Beseitigung radioaktiver Abwässer zugeführt werden muß. Für orientierende Messungen kann es auch empfehlenswert sein, zur Beobachtung der Waschwasseraktivität der Waschmaschine ein kleines Misch- und Meßgefäß (am besten aus PVC) mit Tauchmeßsonde (SCHANZE 1959 u. 1961).

Nach dem Trocknen der dekontaminierten Wasche ist sie vor dem Verlassen der 'aktiven Wascherei' sorgfältig mit einem Monitor zu prüfen, ob eventuell noch Restaktivität zurückgeblieben ist. Dazu ist bei größeren Waschemengen und bei Bettzeug ein besonderer Wasche-Prüfungsmonitor zeitsparend und zweckmäßig. Bei einem solchen, in Bild 4 gezeigtem Gerät wird die

Wasche durch den Meßrahmen (Innenmaße  $10 \times 100$  cm) geführt, wo sie von sechs gegen Umgebungsstrahlung abgeschirmten dünnwandigen Zahlrohren von oben und unten abgetastet wird. Beim Vorhandensein einer Restkontamination, die größer ist als der im Anzeigergerät vorgewählte Wert, wird noch ein akustisches und optisches Signal gegeben. Weiterhin ist noch eine Handsonde zum Zwecke der genauen Lokalisation einer festgestellten Kontamination am Anzeigergerät angeschlossen.

Zeigt sich nach dieser Schlußprüfung noch Kontamination, so ist der Waschvorgang, für den übrigens normale Waschmittel verwendet werden, zu wiederholen.

## ZUSAMMENFASSUNG

Ein Strahlenschutzwagen wird beschrieben, der alle Dinge, die bei einem Unfall mit offenen radioaktiven Stoffen in Isotopenlaboratorien benötigt werden, enthält. Anleitungen zur Dekontamination und zum Vorgehen nach einem Unfall mit Radioisotopen werden auch gegeben. Weiterhin wird die Behandlung radioaktiver Wasche erläutert und eine aktive Wascherei beschrieben.

## SUMMARY

An accident trolley is described that contains everything needed if an accident with radioactive materials occurs. Instructions for decontamination are given and measures to be taken after mishaps with open isotopes are recommended. Cleansing and treatment of laundry that has been contaminated with radioactive material are discussed and an active laundry is described.

## RÉSUMÉ

Description d'une voiture de secours contenant tout le matériel nécessaire en cas d'accident libérant des substances radioactives. L'auteur donne des indications pour la décontamination et recommande les mesures à prendre après les accidents libérant des isotopes. Il explique comment traiter le linge radioactif et décrit une blanchisserie active.

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